THE JOURNAL

of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 147, NO. 1 — CHICAGO, ILLINOIS — SEPT. 1, 1951

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PAROXYSMAL ABDOMINAL PAIN

A FORM OF EPILEPSY IN CHILDREN

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Very little is known in man about the cerebral representation of the vasomotor and visceromotor mechanisms and their sensory counterparts. However, animal experimentation points to the existence of neuronal chains concerned with these functions at almost all levels of the brain, and clinical evidence exists as to their involvement in disease and dysfunction of the brain.

Dysfunction of cortical and subcortical structures in man in many instances leads to changes in the electroencephalogram. In many cases diencephalic and particularly thalamic disorders have been known to influence the cortical electrical activity. This is particularly true for epileptic manifestations in the widest sense.

The present study deals with a group of patients in whom paroxysmal visceral symptoms were the presenting complaint. The first 12 of these patients were seen about 10 years ago at the Babies Hospital and the pediatric service of the Vanderbilt Clinic.[1] During the intervening 10 years we have added 19 cases to the group, and gradually the clinical picture has become clearer.

All the children have said they had abdominal pain that in almost all instances has been periumbilical and epigastric. In some instances it radiated to the lower quadrants or the flanks. It has practically always been sudden in onset, of a severe nature, and has been described as colicky or knifelike. The pain lasted a few minutes to several hours. In several cases bouts of pain recurred several times in the course of two or three days. The pain has been associated in most instances with other gastrointestinal symptoms, such as anorexia, nausea, vomiting, diarrhea, or, less frequently, constipation. Sixteen of our patients fell asleep after an attack of abdominal pain no matter what time it occurred and slept for several hours even in the middle of the day. Twelve patients said they experienced headache, lateralized in two cases, associated with an attack. Nine patients had fever with the attacks, and seven had drooling and sweating.

In addition to the attacks of abdominal pain, many of the children have shown abnormal traits. In 17 there was an abnormal degree of irritability and other behavior disorders. In 12 there were multiple vasomotor disturbances, such as blanching, flushing, and lability of blood pressure. In two of the children peripheral vasoconstriction and cyanosis have been observed between attacks. In four patients some of the attacks have been associated with cyclic vomiting, and the children were admitted in severe states of dehydration and acidosis.

The clinical symptoms were not explained by the usual diagnostic procedures, the results of which were negative or showed insignificant changes. On the other hand, the paroxysmal nature of the attacks, the post-paroxysmal sleep, and the fact that they occurred in groups suggested a similarity in pattern with epilepsy and, considering the possibility of a cerebral origin for the syndrome, a systematic study of electroencephalographic changes was made. As a result of these studies it was found that all the patients but one showed grossly abnormal cerebral electrical activity.

CLINICAL DATA

Thirty-one patients were seen in this series. There was no sex preponderance, there being 16 boys and 15 girls in the group. Twenty-six of the children were normal, spontaneous, full-term deliveries. One had been born prematurely, weighing 4 lb. (1,814 gm.) at birth. One was overterm, and delivery necessitated the use of high forceps, which resulted in a permanent left temporal scar. In one case internal version with forceps was needed. In two other instances prolonged labor was terminated by forceps delivery. Early development was reported as delayed in four children. The onset of the attacks could usually be traced to early infancy. In a few they began after the age of 6 yr. and in one after 11 yr. The patients had the usual childhood diseases without complications, except for one case of unspecified encephalitis and two

Aided by the Isador Abrahamson Fellowship from the Mount Sinai Hospital, New York City, and the Dazian Foundation (Dr. Cohen).

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cases of pertussis encephalitis. In two instances the onset of the syndrome occurred just after the illness. In one patient attacks of abdominal pain started 2½ years after an attack of pertussis encephalitis. However, this patient had had a series of convulsive attacks at the time of the encephalitis. Convulsive phenomena preceding or accompanying the onset of abdominal pain were also seen in three other children. One of these had a single unexplained convulsion a year prior to the onset of abdominal pain. A third patient had psychomotor attacks for about eight years preceding her first attack of abdominal pain. The onset of grand mal, petit mal, and psychomotor equivalents coincided with the onset of abdominal pain in still another child. No other significant features were established in our patients' past histories. In the family histories of the children epilepsy occurred three times; behavior problems, three times, and migraine and abdominal pain, each twice. Two of our patients were sisters.

Except for the multiple signs of autonomic imbalance, physical examination revealed few abnormalities. Members of the group as a whole appeared underdeveloped, immature, and small for their chronological age. However, no clearcut abnormalities were found except for a facial tic in one patient and shortening of the left upper extremity—associated with a Davidoff-Dyke-Masson deformity of the skull—in another. The mental examination deserves to be mentioned only in two respects. First, intelligence quotients were found to be scattered over a wide range from 70 to 160 (Wechsler-Bellevue test); second, there was a high incidence of abnormal irritability and behavior disorders that has already been mentioned. No overt psychotic manifestations were found in any member of the group.

Of the diagnostic procedures performed in this group, routine laboratory studies of blood, urine, stool, and, in a few cases, of the spinal fluid were negative. Tuberculin tests were done in 26 patients and were found positive in two. X-rays of the skull were obtained in eight patients, in four of these in conjunction with air studies. In one of these an enlargement of the left lateral ventricle was found; in another the findings were those of the Davidoff-Dyke-Masson syndrome. Pyelograms in 24 patients and gastrointestinal series in 20 failed to show any significant structural changes. However, transient abnormally fast peristalsis and pylorospasm were each seen three times. In one patient the two occurred together.

Electroencephalographic studies showed definite abnormalities in 30 patients and a "borderline normal" record in one. A breakdown according to frequency and pattern of the electroencephalograph observations revealed that of the 30 patients with abnormal activity the records were basically normal in two, while 28 had basically slow activity ranging from 2 to 7 cps; in addition, 16 of these had rapid or spike activity or both (15 to 30 cps), and four had frank spike-and-wave bursts. In response to hyperventilation all but one, who was unable to cooperate, had further slowing and increase in amplitude of the slow activity, usually with the appearance of synchronous bursts. The same type of response to hyperventilation was found in the two patients with basically normal electroencephalograph activity. No clearcut focal signs were found in any of our records. It should be noted that none of these patients had electroencephalographic studies performed during an actual attack of abdominal pain.

Synchronous discharges of high voltage slow waves and spike-and-wave bursts are the two main criteria for epileptic activity. An over-all incidence of abnormal electroencephalographic activity, both specific and nonspecific, of almost 97%, as found in our patients, must be considered positive evidence of the cerebral and presumably paroxysmal origin of this particular disease entity. This figure compares well with those obtained in highly selected groups of established epileptics in our own and other laboratories.[2] The observations in normal and nonepileptic children of the same age groups similarly tested differ significantly from those presented here.

In a recent case, not included in this series, the clinical and laboratory picture presented physiological evidence of a specific cerebral mechanism by which transient paroxysmal abdominal pain can be produced. A girl of 15 said she had headache and severe migratory abdominal pain. On repeated neurological examination nystagmus associated with inability to perform upward gaze was noted on one occasion. The electroencephalogram showed synchronous bifrontal discharges of high voltage, 3 per sec. activity (Fig. 1). During one of her attacks of pain a gastrointestinal series was performed. On this occasion a transient episode of intussusception of the terminal ileum was observed. One loop of ileum in the right abdomen showed a localized narrowing in which two longitudinal mucosal folds could be recognized. These folds could be identified as extending into a slightly dilated adjacent portion of the ileum, where the transversely arranged mucosal folds surrounded the thinned longitudinal folds. This appearance is characteristic of an ileo-ileal intussusception (Fig. 2). This and two similar areas were observed in the same examination. But there was no evidence of intussusception on an examination repeated eight days later, at which time the patient was asymptomatic.[3]

COURSE

Twenty-one patients were followed for periods up to 10 years. Among these were eight of the original group of 12 patients. Two others of this group died, one in an accident, the other one of mesantoin® (3-methyl-5,5-phenyl-ethyl hydantoin) intoxication during a period of intractable grand mal epilepsy.

In nine of the 21 children attacks of abdominal pain subsided completely at adolescence. In five others distinct improvement was found in that the attacks have recurred much less often and have been much milder. In five others the condition has become worse.

Frank epileptic manifestations occurred in nine of the entire group of 31 patients. Four, as stated previously, had attacks preceding the onset of paroxysmal abdominal pain. All four still have epileptic seizures, three with abdominal pain as aura, while the last one of this group no longer has attacks of abdominal pain in any form. Five other patients began experiencing epileptic seizures

2. Hoefer, P. F. A.; Hoff, H. H., and Pluvinage, R. I. L.: Effect of Anticonvulsant Therapy on Electroencephalogram of Patients with Idiopathic Epilepsy, Tr. Am. Neurol. A. 72: 185, 1947.

3. Courtesy of Dr. Lois Collins of the Department of Radiology, College of Physicians and Surgeons.

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several years after the onset of the abdominal pain syndrome. To this group belongs a patient who died of mesantoin® intoxication. Another patient had petit mal attacks that have since subsided. The remaining three still have seizures but no abdominal pain.

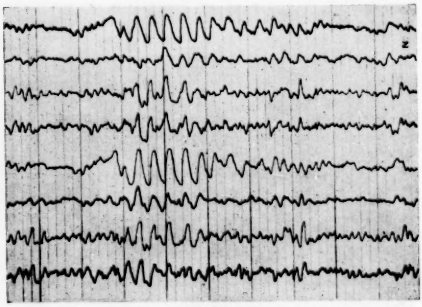

Fig. 1.—G. H., 14 years of age. Especially during hyperventilation the record shows high voltage 3 per sec. activity with bifrontal preponderance often in synchronous bursts. The tracings are from the right frontal, right temporal, right parietal, right occipital, left frontal, left temporal, left parietal, and left occipital areas.

Electroencephalographic records were obtained at intervals in 20 patients of the group that was followed up to 10 years. The electroencephalograms of eight patients were normal, three were mildly abnormal, and nine persistently abnormal. In six of the persistently abnormal records 3 cps activity was seen in response to hyperventilation, and one showed spike-and-wave groups. These follow-up studies could be fairly well correlated with the clinical course, in that normal or near-normal records were obtained in patients in whom the symptoms had subsided.

Anticonvulsant therapy was tried in eight of the patients who had abdominal pain not associated with clear-cut epileptic attacks. However, in no patient in our group was therapy administered for a sufficiently long period to allow proper evaluation. In a few instances an impression of temporary improvement has been recorded.

REPORT OF CASES

CASE 1.—B. M., a 6-year-old girl, was first seen at the Vanderbilt Clinic on Oct. 23, 1945. During the previous two years she had had between 15 and 20 episodes of abdominal pain associated with nausea, vomiting, and malaise. The attacks recurred every five months, lasting five minutes to several hours, and 12 or more occurred during a period of two or three days. A typical episode resembling status was described in May, 1946, as follows:

The patient, who had been perfectly well before going to bed, was awakened by an attack of abdominal pain at 1 a. m. She had seemed to have been having a nightmare prior to this. She then cried out and said she had frontal headache. Almost immediately, sharp, cramping periumbilical abdominal pain followed, with the patient doubled up and screaming. The pain lasted about five minutes, during which time she vomited her evening meal. After five minutes relief she had another attack, this time lasting five minutes. She then fell asleep but was again awakened at 4 a. m. with another series of three or four paroxysms of pain and vomiting. The patient appeared to be stuporous and fell asleep until 6 a. m., when the attacks recurred.

Six weeks prior to this episode the patient was seen to "snap back" and become "stiff" during a vomiting spell. She became deeply stuporous for 10 min. and could not be awakened. She then went into a deep, heavy sleep from which she could be aroused only with difficulty.

Past history revealed an attack of pertussis at the age of 4 years immediately preceding the onset of her attacks of abdominal pain.

Her family history was noncontributory, except that a baby sister of 13 mo. had "breathholding" spells.

Examination: The patient was thin, normally developed, retiring, and fearful. She had considerable abdominal spasm and pain. The general physical and neurological findings were otherwise normal. Urinalysis showed the presence of acetone (3 +). The electroencephalogram record revealed numerous high voltage synchronous spike-and-wave bursts preceded by brief showers of spikes (Fig. 3*A*). There were no other positive laboratory observations.

Course: The patient's acute symptoms subsided spontaneously, and her urine became acetone-free on supportive therapy. Subsequently, her attacks began to come at shorter intervals. There was no clearcut relief on various anticonvulsant drugs [phenobarbital, diphenylhydantoin (dilantin®), trimethadione (tridione®), mesantoin,® and mephobarbital (mebaral®)], though at one time she was reported to be free of symptoms for a period of nine months. Recently two additional symptoms have developed: "tremor of the hands" and a variety of psychomotor episodes, including fully creditable fugue states, forgetfulness, and the like. In addition, she showed various behavior disorders, moodiness, scratching or biting other children. Her last electroencephalogram, taken in February, 1950, when she was 10½ years old, was only mildly abnormal and without convulsive patterns (Fig. 3*B*).

CASE 2.—T. L., a boy 8 years old, entered the Babies Hospital on July 8, 1940. He said he had had frequent episodes of abdominal pain for one year. Onset occurred during convalescence from pneumonia, after which attacks recurred repeatedly from one to five times a week. He had an aura of a "noise in the head" or transient headache. This was followed by rather severe periumbilical pain lasting a few seconds and associated with rigidity of the hands and momentary loss of consciousness. The patient then fell asleep for about 10 min. and on awakening was clear mentally but had a rather "glassy stare" in his eyes.

Fig. 2.—Ileo-ileal intussusception indicated by arrow. See x-ray report in the text.

Examination: The patient was well nourished and well developed, overactive, and combative. The general physical and neurological findings were normal. Tuberculin test (0.1 mg.) was positive. A chest x-ray was reported as negative. Gastrointestinal series revealed no evidence of organic disease of the gastro-

intestinal tract, but there was some decrease in tone of the lower small intestine, a low cecum, and hypomotility of the ileum.

The electroencephalogram showed medium to high voltage, rapid activity in both frontal areas and somewhat less in the parietal areas. Irregular medium 4 to 5 per sec. activity was seen mostly in the occipital areas. Occasional synchronous bursts of high voltage 3 to 4 per second activity appeared, especially with hyperventilation (Fig. 4*A*).

Course: Abortive grand mal (slight convulsive movements of both arms and right leg with loss of consciousness) later developed in the patient. Abdominal complaints decreased in frequency and intensity, and the patient had only five mild attacks in one year, although he had stopped taking anticonvulsant medication. After diphenylhydantoin was reinstituted, the patient was symptom-free for several months, and attacks usually occurred when medication was omitted.

An electroencephalogram taken at this time, March, 1945, showed considerable improvement. It was still abnormal but revealed no paroxysmal patterns. The record was diffusely irregular, with a small amount of rapid activity limited to the frontal leads and a large amount of slow 4 to 6 per sec. disorganized activity, both mostly of low amplitude. There was not much change with hyperventilation (Fig. 4*B*). No subsequent electroencephalographic studies were done.

Frank grand mal uncontrolled by anticonvulsant therapy then developed in the patient. He was again hospitalized because mesantoin® sensitivity and aplastic anemia with septicemia developed. He continued a downhill course and died in February, 1948.

The autopsy, including gross and microscopic examination of the brain, showed evidence of acute toxic-infectious disease. There were diffuse cortical changes consistent with severe grand mal attacks and no signs of any focal lesion.

CASE 3.—W. S., a 12-year-old boy, was seen at the Vanderbilt Clinic in January, 1940. At the age of 7 years he began to have attacks of headache, buzzing in the ears, nausea, and vomiting with abdominal pain every two to four weeks. Each episode lasted 30 min. and was followed by sleep for four or five hours. He was perfectly well on the next day. Past history was noncontributory except for food allergy (hives) and one episode of sleepwalking.

Fig. 3.—*A*, B. M. 6½ years of age. Synchronous burst of high voltage somewhat atypical 3 per sec. spike and wave activity preceded by a brief shower of spikes. The end of the run shows mostly wave activity. Time for 1 sec. and calibration for 50 μv. are indicated. *B*, B. M., 10½ years of age. The record is mildly irregular, with some slow activity in both frontal areas. (In both strips the tracings are from the right frontal, right parietal, right occipital, left frontal, left parietal, and left occipital areas.)

Examination: The general physical and neurological findings were normal. Electroencephalographic studies revealed a striking response to hyperventilation with almost immediate slowing to synchronous, high voltage 3 per sec. waves from a reasonably normal baseline. On several occasions synchronous bursts of 2 to 3 per sec. activity were seen. This response came on within seconds (Fig. 5).

Course: On diphenylhydantoin the patient had no attacks for almost three months. The drug was then discontinued for a similar period, and during this time he had six attacks. Diphenylhydantoin therapy was resumed, and again he was free of symptoms while he was receiving this medication. Subsequently, the attacks subsided spontaneously, and he was discharged without any further therapy. The patient did well in his studies, having won a four-year scholarship at high school. On July 10, 1942, while delivering newspapers on a bicycle, he was hit by an automobile and killed.

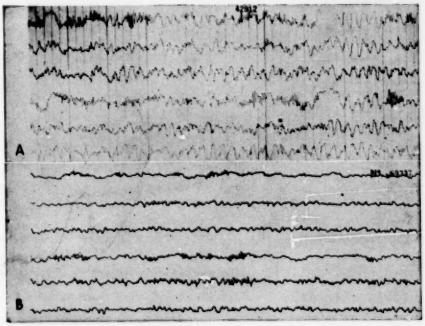

Fig. 4.—*A*, T. L., 8 years old. The record shows two striking abnormalities. Mostly medium voltage 25 per sec. activity is seen in both frontal areas, while irregular mostly medium voltage 4 to 5 per sec. activity occurs in the other leads. On one occasion a synchronous burst of slow activity is recorded in all the leads. *B*, T. L., 13 years of age. The record is irregular, with some persisting rapid activity in the two frontal areas and low voltage disorganized slow activity in the other leads. The time and calibration and sequence of tracings is as in figure 3.

CASE 4.—C. McC., 7-year-old boy, was first seen at the Vanderbilt Clinic in January, 1936. He had a history, starting at the age of 2½ years, of severe frontal headaches frequently lateralized over the right eye and always associated with nausea, vomiting, and abdominal pain. The attacks, which recurred every two months, were followed by sleep for a few hours, and when he woke the patient vomited with relief of the headache. At 11 years he had three episodes of nausea and fainting while in church. In addition, he was very restless during sleep, "talking and raving," and sleepwalking. In March, 1939, he was treated for a fractured elbow incurred in a fall during a somnambulistic episode. Past history suggested allergic rhinitis for one year when he was 10 years old. Family history was significant only in that his mother had hay fever.

Examination: The patient was thin, well developed, irritable, and restless but cooperative. The general physical and neurological observations were normal. Electroencephalogram showed in the first part of the record quite irregular activity, with a good deal of poorly formed 5 to 7 per sec. activity of medium voltage, and low voltage 15 to 20 per sec. activity. Occasional synchronous bursts of slow activity were seen. There was a striking response to hyperventilation with bursts and long runs of very high voltage 2 to 3 per sec. waves. The patient's symptoms gradually subsided, except for occasional mild frontal headaches and persistent irritability. When last seen in February, 1950, he was a tall, asthenic 21-year-old man with a responsible job. He had completed one year of college. An encephalogram taken at this time revealed mild irregularities especially with hyperventilation, but the record was otherwise normal.

CASE 5.—E. T., a girl of 8 years, was seen at the Babies Hospital in November, 1940. Since the age of 1½ years and after a fall she had experienced severe, generalized periumbilical, and epigastric pains. The attacks varied in frequency between once a week and once a month, were followed by pallor, yawning, and malaise, and were associated with nausea, vomiting, constipation, and temperature to 104 F. The abdominal pain was cramp-

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like at the onset of an episode, then increased until it felt "like knives sticking"; and her abdomen became rigid and extremely tender. The pain gradually subsided, only to recur repeatedly. The whole episode usually lasted a day, and during this time the patient felt drowsy and occasionally went into a deep slumber. On the day prior to an attack the patient's face was flushed.

Past history revealed allergy to various foods, including chocolate, but dietary restrictions and "injections" did not relieve her symptoms. An appendectomy was performed when she was 3½ years old.

Examination: The patient was a small, thin girl who was well oriented and cooperative. The pulse was 104, the blood pressure was 118/72. A soft systolic murmur was heard at the apex. Gastrointestinal series showed reflex pylorospasm. When repeated at a later date it was reported to be negative. The electroencephalogram record was mildly abnormal. Single, large, slow waves of frequencies between 3 and 4 per sec. were seen in both occipital leads, occasionally with a vague suggestion of a slow spike and wave pattern. In the two frontal leads short bursts of fast activity were noted. With hyperventilation a moderate increase in incidence of the slow waves was noted, and on one occasion a short burst of moderately high synchronous slow waves was seen.

Course: The patient's symptoms have continued without significant improvement, although the abdominal pains are said to be less severe. A trial of antihistaminics brought no relief. Her subsequent electroencephalograph records, however, have all been essentially normal with no response to hyperventilation. Although 18 years old, the patient is a small, underdeveloped girl who looks like one of 14.

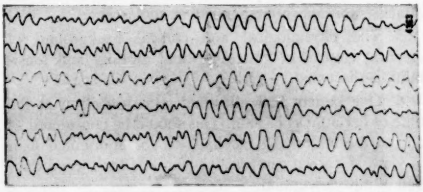

Fig. 5.—W. S., 12 years old. During hyperventilation the record shows high voltage 3 per sec. activity. Tracings are from the right frontal, right parietal, right occipital, and the left frontal, left parietal, and left occipital areas.

CASE 6.—A. H. B., a 12-year-old girl, was first seen at the Vanderbilt Clinic in November, 1941. At 2½ years she began to have occasional episodes of falling to the floor with rolling of the eyes. These were followed by spells consisting of change of expression and pallor of the face, the patient lying down quietly and becoming limp. These attacks occurred during the next nine years every 12 to 15 mo. and were preceded by an aura of dizziness and "blackout." Since December, 1940, the episodes have increased in frequency to three times a month, starting with severe periumbilical, cramplike abdominal pains associated with anorexia and followed by sleep for two hours.

Past history was significant in that the patient was premature, weighing 4 lb. (1,814 gm.) at birth. She had had infantile diarrhea and marasmus. Development was delayed, the patient did not talk until she was 3 years old, and enuresis persisted until that time. She was allergic to chocolate. Family history, extending back to both maternal and paternal grandparents, revealed epilepsy, prostitution, indigence, feeblemindedness, shiftlessness, and capital crime. All the patient's ten siblings were feebleminded or of borderline intelligence.

Examination: The general physical and neurological findings were normal. The electroencephalograph record showed fair alpha activity on the right, poor on the left side. A good many slow waves (3 to 5 per sec.) of moderately high voltage were seen in both occipital leads but definitely more on the left side. With hyperventilation a distinct increase in amplitude occurred with a definite additional slowing. Synchronous bursts of very high voltage irregular 3 to 5 per sec. waves were seen repeatedly, lasting for more than six seconds. In addition, runs of the same type of waves occurred in either occipital lead alone but again definitely more on the left side.

Course: The patient's attacks subsided on diphenylhydantoin. When medication was discontinued in June, 1942, she remained free of attacks until November, 1946. At that time the attacks recurred, and she was again placed on diphenylhydantoin, 0.1 gm. twice a day. Episodes were reduced in number to about two a year. In the summer of 1949 she had a grand mal seizure preceded by an aura of abdominal pain. The patient is now a 21-year-old housewife, who is short and obese, and shows much irritability and vasomotor lability. Her most recent electroencephalogram record is somewhat disorganized without being clearly abnormal. There is a persistent difference between right-sided and left-sided alpha activity. A few runs of disorganized 5 per sec. activity are seen, especially on the left side, at the end of and after hyperventilation.

COMMENT

Fulton, Kennard and Watts [4] found that stimulation of the rostral portion of the premotor area causes increase in peristalsis. Extirpation of the same region leads to slowing of visceral motility and in some instances intussusception, as shown by Watts and Fulton.[5] Mettler and associates [6] made similar observations and found ulcers of the stomach at autopsy in animals with long-standing ablation of the frontal lobes. More recently, Spiegel and associates [7] found that gastrointestinal motility in dogs could be influenced from areas 5 and 3 in addition to the premotor area 6 and occasionally area 4 but in their experience from no other point of the cortex. Correll, Greenberg and Pool [8] produced massive intussusception as the result of repeated bilateral stimulation of the cingular gyrus just above the splenium of the corpus callosum in one unanesthetized cat. The same animal had generalized convulsions in response to the stimulation on this occasion.

While the experimental observations were concerned with the results of cortical stimulation and ablation, Cushing [9] and Grant [10] reported gastric and duodenal ulcers in patients with tumors of the interbrain.

In the realm of epileptic phenomena, epigastric pain as an aura preceding grand mal attacks was described by Gowers,[11] who in his book "The Borderland of Epilepsy" differentiated it from vagal and vasovagal attacks, epigastric sensations of oppression or fullness. Oppenheim [12] in discussing earlier authors' concepts of "larval" epilepsy including "gastric disturbances" thought the evidence was "most uncertain." Patrick and Levy [13] described paroxysmal abdominal pain, mostly in infancy and childhood, as a "fore-runner" of true grand

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mal seizures in 13 out of 500 cases, in six of which it became the aura. Watts and Frazier [14] described the cases of two patients, one a boy of 8 years, in whom nausea, epigastric distress, and vomiting were often substituted for true convulsive seizures. Wechsler [15] recognized abdominal pain separate from nausea and projectile vomiting as a symptom of brain tumor in a small series of verified cases. Penfield [16] described epigastric pain as an unspecific aura associated with many different types of seizures, such as autonomic, petit mal, Jacksonian, and hallucinatory. In some of these the localization of the subsequent seizures was presumably diencephalic, in others cortical: temporal, central, or parietal. According to Penfield, epigastric aura has no localizing value.

Robinson [17] studied 100 epileptic patients by gastrointestinal x-ray series. Twenty-three of these patients had some type of gastrointestinal aura. However, only three had gastrointestinal abnormalities. Eleven others showed structural or functional abnormalities of the gastrointestinal tract but had no gastrointestinal aura.

Moore in several recent publications [18] has described several cases of patients with symptomatic or in one case idiopathic attacks of abdominal pain of cerebral origin, some with electroencephalograph findings suggestive of paroxysmal disorder. None of his patients were infants or children.

Delay [19] has recently described a patient 19 years of age, a congenital syphilitic in whom abdominal pain in attacks, vasomotor changes and an abnormal electroencephalogram with suggestive left temporal focus developed. This patient had striking relief from his attacks on anticonvulsant medication.

Lambert [20] in a study of 25 children with abdominal pain stresses psychodynamic mechanisms in preference to an organic epileptic etiology in spite of the fact that 12 of his patients had abnormal electroencephalograms, three of these with frank convulsions. Furthermore, two of the children had evidence of "spastic colon" by x-ray studies and one had Sydenham's chorea.

Our reasons for including the syndrome described in this study among the manifestations of epilepsy in the widest sense may well be reviewed at this point. The attacks of abdominal pain are episodic in nature and often grouped in a status pattern. In many instances the attacks are followed by episodes of sleep of several hours' duration, often in the middle of the day. Several of our patients had brief periods of unconsciousness or other seizure fragments associated with the attacks of pain. Abnormal electroencephalographic patterns were found in 97% of our patients in "interseizure" records. Finally, nine of our patients had frank convulsive seizures.

Response to anticonvulsant therapy in patients without frank convulsive manifestations has been equivocal in our experience. However, Schwentker and Livingston [21] recently described a group of 29 children with abdominal pain as a manifestation of epilepsy. Fourteen of the patients had postictal sleep, 11 of these were markedly benefited by treatment with diphenylhydantoin. None of the others were helped by anticonvulsant medication.

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SUMMARY

This report is a follow-up study of a group of children suffering from abdominal pain of cerebral origin and considered to be an epileptic phenomenon.

A total of 31 patients were observed. The clinical picture includes numerous autonomic features, especially vasomotor phenomena.

1. Pathological electroencephalographic findings were obtained in 30 cases.

2. Postictal sleep was seen in 16 cases.

3. Nine patients had clearcut convulsive phenomena at one time or another.

4. In nine other patients without convulsions the attacks subsided spontaneously at adolescence.

5. The physiological and clinical background of cerebral control of gastrointestinal motility and sensibility is discussed.

6. One patient had intestinal intussusception at the time of her attacks of pain. This should be considered as one of the underlying mechanisms for abdominal pain in view of known cerebral mechanisms for the production of intussusception.

622 W. 168th St.

William Beaumont.—The fame of William Beaumont is well established in American scientific lore; the school-boy whose participation in the science of physiology is, at best, in the hazy future has heard in some detail of this energetic doctor who carried out experiments on a man with a hole in his stomach in a backwoods settlement in upper Michigan more than a hundred years ago. . . . Beaumont's ancestors were stalwart New Englanders. . . . He grew up in a home where civic and religious obligations were taken seriously and in addition he had the advantages of excellent local schooling. . . . He . . . settled in Champlain, New York, where for three years he taught the village school. He entered into the social life of the town and, after deciding to become a doctor, read avidly in borrowed medical books. In 1810 he began the serious study of medicine with Dr. Benjamin Chandler in St. Albans, Vermont. His first-hand experience in anatomy consisted of the dissection of every amputated arm or leg he could secure; he urged autopsies at the death of his patients and from these, too, he learned anatomy. He secured his license to practice medicine in 1812 and very soon thereafter joined the U. S. Army at Plattsburgh. . . . Beaumont took part in the War of 1812, seeing service as a military surgeon from February, 1813, to August, 1814, largely in the region around the mouth of the Niagara River and in Plattsburgh. Even before leaving Plattsburgh and throughout the campaign in 1813 he kept voluminous notes bearing on his medical experiences—the therapeutic and surgical treatment employed and, wherever possible, the results obtained, all in the minutest detail.—Arthur H. Smith, William Beaumont (November 21, 1785—April 25, 1853), *Journal of Nutrition*, May, 1951.

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TERMINAL BRONCHIOLAR OR "ALVEOLAR CELL" CANCER OF THE LUNG

REPORT OF THIRTY-THREE CASES

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and
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At Memorial Hospital we have noted in the past several years a definite and rapid increase in the incidence of cancer of the lung. At the same time, a corresponding increase in the number of lesions that we classify as "terminal bronchiolar or alveolar cell cancer of the lung" has been reported by the department of pathology.

Malassez,[1] in 1876 was the first to describe the multiple, nodular form of alveolar cell carcinoma. At autopsy both of his patient's lungs were found to be studded with pea-sized nodules, but the bronchi themselves were free of tumor. Microscopic study of the lesion revealed the alveoli to be lined with a cylindrical, cuboidal and flat epithelium. The peribronchial lymph nodes contained metastatic tumors. In 1903 Musser[2] described a diffuse form of this type of lung cancer. This is a rarer type, which may involve a single lobe or an entire lung, and it may simulate lobar pneumonia in the stage of gray hepatization. Musser also described satellite nodules in the opposite lung.

CLINICAL ASPECTS

The clinical material for this report is a series of 33 histologically proved cases of terminal bronchiolar cancer of the lung found in a review of 1,585 malignant lung lesions at Memorial Hospital. The first case of terminal bronchiolar cancer encountered in this series appeared in 1932. Twenty-one patients with this type of disease have been seen by us in the past five years, 18 in the past two years, and 13 in the past year. This would seem to indicate that the disease is now more readily identified by the pathologist and that in many of the earlier cases lesions may have been incorrectly classified as mesothelioma, adenocarcinoma, anaplastic carcinoma or metastatic carcinoma. The true incidence of this disease at our hospital, therefore, cannot be accurately determined. There has been a rapid increase in cases of lung cancer at Memorial Hospital in recent years, and a proportionate increase in the number of carcinomas of the alveolar type is to be expected.

The symptoms and clinical course of terminal bronchiolar carcinoma differ slightly, but definitely, from those recorded for the commonest types of bronchogenic cancer. The disease varies in aggressivity: death may occur within a few months after the onset of symptoms, or, as in the case of two of our patients, who are alive and well more than five years after operation, the disease may prove to be relatively localized and benign. There was definite evidence of metastases in all the 19 patients who died. Brain metastases were noted in two patients, and in five there was roentgenographic evidence of bone metastases. In 70% of the cases of terminal bronchiolar carcinoma, the history on admission pointed to a primary lung disease. Fourteen of the 33 patients complained of symptoms now recognized as suggestive or even pathognomonic of cancer of the lung. The history of eight other patients simulated that of an inflammatory type of pulmonary disease; four patients complained of symptoms that indicated a generalized disease, such as Hodgkin's granuloma. Five patients had no symptoms, the tumor of the lung being discovered in routine chest roentgenograms taken for tuberculosis survey studies or in routine preemployment films. Carcinoma of the esophagus was suspected in one patient, and the remaining patient had symptoms of cardiac failure.

In this series of 33 cases, the average age of the patients was 55.6 years and one fourth of them were women. The occupations of the men varied from business administration (in 10 cases) to various types of manual labor, such as plumbing, mechanics and stationary engineering. The women were all housewives. No recognized carcinogenic factor was elicited in a study of the histories of these patients. Five did not smoke, eight were moderate smokers and 10 were heavy smokers. Family histories were available for 21 patients, and four of these reported cancer in other members of the family. History of an attack of disabling influenza, 20 to 30 years before the current illness, was described by two patients. Eleven gave histories of previous lung disorders. One probably had had pulmonary tuberculosis 25 years before the present illness, and two reported having had pleurisy. Five had been told they had pneumonia in the six-month period prior to hospitalization.

Presenting Symptoms.—Pain and cough were the commonest symptoms. Bloody sputum was noted in nine cases, but only one frank hemoptysis was recorded. The average duration of symptoms before admission was four months.

Physical Findings.—No objective evidence of tumor was found on physical examination of 13 of the 33 patients. Physical signs indicated chest disease in 13 instances. Five patients had palpable tumor metastases in the skin and supraclavicular lymph nodes, and one, although in the terminal stage of the disease, had no physical signs of cancer. Pleural effusion was recorded as present in nine instances, and two patients had clinical signs of brain metastases.

Roentgenologic Findings.—In one instance the x-ray studies were considered to be negative, and yet in this case an exploratory thoracotomy revealed a nonresectable setting due to extensive invasion of vital structures by cancer. The commonest roentgenographic finding was

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2. Musser, J. H.: Primary Cancer of the Lung, Tr. A. Am. Physicians **18**: 624-636, 1903; also in Univ. Pennsylvania Bull. **16**: 289-296, 1903-1904.

a single, peripherally located, circular area of increased density, usually 2 to 4 cm. in diameter. This nodule, as in almost any primary lung cancer that occurs away from the hilus, seemed to differ from the usual metastatic nodule in that it appeared to be more irregular, slightly larger, less homogeneous, less sharply outlined and, in

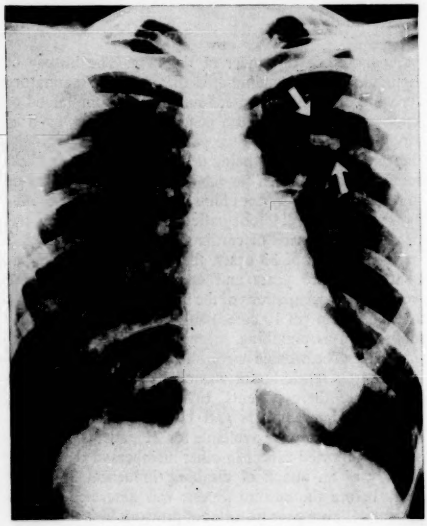

Fig. 1 (case 21).—Roentgenogram showing circumscribed tumor in the left upper lobe.

many instances, less dense. Seven patients had multiple nodules, and the disease was bilateral in several instances. Roentgenographically, the disease in these cases might be confused with pneumonoconiosis, miliary tuberculosis or metastatic cancer. Evidence of fibrosis, however, was absent, and the nodules seemed to coalesce to form infiltrative masses. It is interesting to note that terminal bronchiolar cancer of the lung does not produce a characteristically diagnostic roentgenogram. A roentgenographic diagnosis of malignant lung tumor was made in only 65% of our cases.

Laboratory Data.—In no case was the sputum positive for acid-fast bacilli. Cytological studies were made in 15 cases; six specimens were reported as Papanicolaou Class V (showing conclusive proof of cancer), three as Class IV (positive for cancer), and three others as Class III (strongly suggestive of cancer). In one case, in which a pneumonectomy was done, the preoperative sputum reported as Class V was the only positive evidence on which the decision to operate was based. After operation the sputum was negative, but five months later it was again reported as Class V, and roentgenograms then revealed the presence of multiple metastases in the contralateral lung.

3. Papanicolaou, G. N.: Personal communication to the authors.
4. MacDonald, J. R., and Woolner, L. B.: Cytologic Examination of Sputum and Bronchial Secretion in Diagnosis of Bronchogenic Carcinoma, editorial, Surg., Gynec. & Obst. 88: 676-678, 1949.

Papanicolaou,[3] who made the cytological examinations of the sputum and bronchial washings, has noted that this tumor exfoliates profusely and yields abundant material characteristic of this type of neoplasm. MacDonald [4] also believes the bronchial cell changes to be easily identifiable and characteristic of the disease.

The peripheral blood picture in terminal bronchiolar cancer is not that seen in inflammatory disease of the lungs. The leukocyte count varies between 7,000 and 10,000. The lowest was 3,400 and the highest 14,000. For patients with lung cancer the hemoglobin content was exceptionally high, averaging 13 to 15 gm., and the red cell count averaged 4,000,000.

In 19 cases studied bronchoscopically, the tumor was visualized in three instances and positive histological evidence obtained. Each of the patients was in an advanced, or terminal, stage of the disease, and the biopsies revealed cancer in the submucosal lymphatics. Six patients in the terminal stage were too ill to tolerate bronchoscopy.

BASES FOR DIAGNOSIS

The literature reveals that the diagnosis of terminal bronchiolar carcinoma is most frequently made at autopsy. However, in our series of 33 cases, a clinical diagnosis of terminal bronchiolar carcinoma was made in 22 instances. A combination of tests was used to establish that diagnosis: cytological studies of sputum established the diagnosis in five instances, aspiration biopsies of lung masses, in five, and thoracotomy with

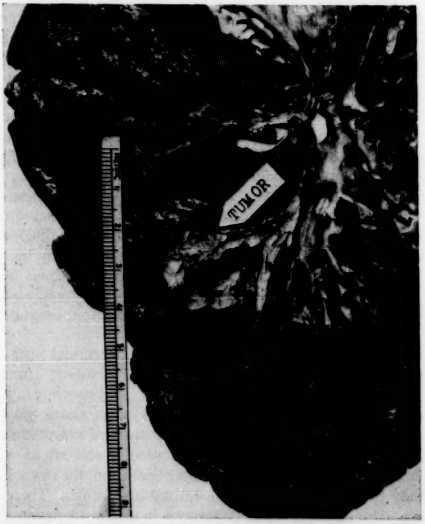

Fig. 2 (case 21).—Operative specimen showing terminal bronchiolar carcinoma.

biopsy, in eight cases. A surgical biopsy of a peripheral lymph node established the diagnosis in four instances. In five cases the clinical and laboratory data indicated a malignant lung tumor, but the exact histological

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diagnosis was made only at the time of necropsy. In the remaining six cases, the diagnosis of lung cancer was established only after post-mortem examination.

TREATMENT

The accepted treatment of terminal bronchiolar carcinoma, as of cancer of the lung in general, is excisional surgery. Radiation therapy may prove a valuable adjunct in palliative treatment in advanced cases. Because of the advanced nature of the disease only symptomatic treatment could be administered to six of the 33 patients. Two patients were misdiagnosed as having metastatic thyroid cancer and received roentgen therapy with some worthwhile palliative effect. The remaining 25 patients received either surgical and/or radiation therapy.

Radiation Therapy.—Nine patients received primary radiation therapy. Four had a hilar mass, three had diffuse nodular disease throughout the lungs and two had a solitary pulmonary mass with pleural effusion containing tumor cells. Six patients died four to eight weeks after completion of therapy, and no appreciable palliative effect was noted in these instances.

In a recent case, surgery was combined with irradiation in a program currently being studied at this institution. The patient was found at the time of thoracotomy to have a locally resectable primary lung tumor but a nonresectable mediastinal mass. A segmental resection of the primary tumor was done, and 56.6 mc. of radon in the form of gold seeds was placed in the mediastinal

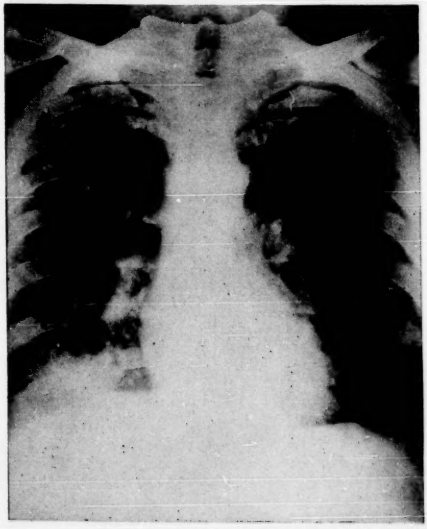

Fig. 3 (case 18).—Immediately preoperative roentgenogram showing diffuse masses in the right lower lobe.

masses under direct vision. This insured direct radiation into the cancer and diminished the undesirable radiation effects on the normal lung tissue. The gold seeds also acted as excellent markers to direct the beam of supplementary supervoltage roentgen therapy. Brain metastasis has since developed in this patient, and roentgen therapy to the brain has given relief of symptoms. The patient is still alive, with evidence of metastases in the brain and cervical lymph nodes.

We realize that nine cases constitute too small a series

Fig. 4.—Photomicrograph of bronchial washing specimen showing characteristic neoplastic cells.

for determination of the efficacy of radiation treatment and also that most of the cancers so treated were inoperable by present criteria and thus clinically far advanced. However, our observations indicate that radiation as a primary means of treatment has little value.

Surgical Therapy.—Sixteen patients received definitive surgical therapy. Ten are living and two of these are alive and well more than five years after excision of their terminal bronchiolar cancer. One was treated by lobectomy and the other by a simple excision of the tumor. Nine of the 16 patients had a complete pneumonectomy, the first of which was done in 1942. Three of these patients died from widespread metastatic cancer 7, 9 and 19 months respectively, after their operations. In four instances metastases were demonstrated in the mediastinal lymph nodes removed at the time of operation. Extensive cancer metastases developed in the remaining lung of one patient. Pteroyltriglutamic acid (teropterin®) and nitrogen mustard therapy had no effect in this case. Five of the nine patients on whom pneumonectomy was performed are living and free of disease.

In one case treatment consisted of a segmental resection of the primary tumor and interstitial radon therapy to the metastatic mediastinal nodes, as previously described. In only two of the 16 patients treated surgically

was the tumor found to be nonresectable at the time of thoracotomy. Both of these patients had direct extension of bulky tumor into the mediastinum.

Sixteen cases may constitute too small a series for determination of the efficacy of a given form of treatment. However, a resectability rate of 87% is more than double that encountered in the usual types of bronchogenic cancer and suggests that this form of cancer of the lung is more amenable to surgical excision. It is also noted that the only patients in our series who survived five years after treatment were those treated surgically (Tables 1 and 2).

Fig. 5.—Specimen removed at operation showing extensive diffuse terminal bronchiolar carcinoma.

TABLE 1.—*Summary of Results of Treatment*

Treatment	Patients Alive More Than 5 Yr. After Treatment	Patients Alive Less Than 5 Yr. After Treatment	Patients Who Died*
Symptomatic	0	1	7
Radiation	0	2	7
Pneumonectomy	0	5	4
Simple excision	1	0	0
Segmental resection plus radiation	0	1	0
Lobectomy	1	2	0
Exploratory thoracotomy plus radiation	0	1	1
Total	2	12	19

* For the 19 patients who died, there was an average interval of 7.6 mo. between the onset of symptoms and death.

PATHOLOGY

Terminal bronchiolar carcinoma occurs almost always in the peripheral portions of the lungs, in either a nodular or a diffuse form. In 21 of the 33 cases, the lesion occurred in the upper lobes, 11 in the left lung and 10 in the right lung. The nodular form was present in 23 instances. The nodules varied in size from a few millimeters to 8 cm. They were discrete and irregular in outline and occasionally had soft necrotic centers. The nodules that occurred near the periphery frequently involved the pleura. The diffuse form of the disease, involving part of a lobe, the whole lobe and sometimes an entire lung, was the predominant feature in 10 cases (30%) of this series. In some instances the multiple nodules seemed to coalesce and form diffuse masses, which grossly gave the appearance of lobar pneumonia in the stage of gray hepatization. In no instance were cavities seen either in the involved area or in the distant lung tissue. Atelectasis was not observed grossly distal to the tumor, nor was suppuration a common finding. In this respect, the gross anatomy of terminal bronchiolar carcinoma differs from the usual bronchogenic carcinoma. Since the primary lesion in terminal bronchiolar carcinoma starts peripherally, atelectasis and suppuration of the distal part of the lung do not occur. Local compression of lung parenchyma by the tumor may produce marginal areas of atelectasis, edema and congestion.

Another gross anatomic characteristic of terminal bronchiolar carcinoma is the absence of involvement of the bronchi. In the early lesions, it is impossible to demonstrate a tumor arising from bronchial epithelium. In the more advanced cases, a bronchus may be invaded by surrounding carcinoma and ulceration may occur. Pleural effusion occurred in nine instances, and in five the effusion was bilateral.

Fig. 6.—Contralateral metastases six months after pneumonectomy.

Metastases.—Metastases were demonstrated in 25 of the 33 cases. The commonest transference was to the

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TABLE 2.—*Summary of Data: 33 Cases of Terminal Bronchiolar Carcinoma*

Case	Year	Age of Patient	Sex of Patient	Presenting Symptoms	Duration, Presenting Symptoms, Mo.	X-Ray Findings (Chest)	Sputum*	Results of Bronchoscopy	Methods of Diagnosis	Location in Lungs	Metastases	Treatment	After Onset of Symptoms
1	1932	62	M	Cough, chest pain	9	Multiple nodules	N	N	Autopsy	Multiple nodules, left lower lobe	Yes	X-Ray	Died 11 mo.
2	1935	35	M	Chest pain	2	Mass filling chest	N	N	Autopsy	Scattered foci, entire left lung	Yes	Symptomatic	Died 2.5 mo.
3	1939	42	M	Dyspnea and dysphagia	4	Multiple nodules	N	N	Biopsy of skin nodule; autopsy	Right lower lobe	Yes	Symptomatic	Died 5 mo.
4	1940	55	M	Cough	5	Hilar mass; peripheral nodule	N	Pos.	Cervical lymph node biopsy	Left upper lobe	Yes	X-Ray	Died 2 mo.
5	1940	61	F	Cough	2	Solitary nodule; pleural effusion	Tb N	Neg.	Autopsy	Right middle lobe	Yes	X-Ray	Died 6 mo.
6	1940	55	M	Loin pain	2	Hilar mass	N	Neg.	Autopsy	Left upper lobe	Yes	X-Ray	Died 7 mo.
7	1942	59	M	Chest pain	1.5	Hilar mass	Tb N	N	Thoracotomy; aspiration biopsy	Left lower lobe	No	Pneumonectomy	Died 19 mo. postoperatively
8	1943	59	M	Dyspnea	1	Pleural effusion	N	N	Autopsy	Entire left lung	Yes	Symptomatic	Died 3 mo.
9	1943	48	M	Back pain	6	Hilar mass	N	N	Autopsy	Right hilar area	Yes	X-Ray to bone metastases	Died 11 mo.
10	1943	41	F	Pneumonia	6	Solitary mass	N	N	Thoracotomy	Right lower lobe	No	Lobectomy	Alive and well after 5 yr.
11	1944	50	M	None	..	Infiltrative mass	N	N	Thoracotomy	Left upper lobe	No	"V" excision tumor	Alive and well after 5 yr.
12	1944	51	M	Pneumonia	5	Multiple nodules	N	N	Autopsy	Right and left lungs	Yes	Symptomatic	Died 6 mo.
13	1945	28	M	Shoulder pain	6	Mediastinal mass	N	N	Autopsy	Left upper lobe	Yes	X-Ray to metastases	Died 16 mo.
14	1947	57	F	Pain, cervical spine	10	Pleural effusion	N	Neg.	Autopsy	Left upper lobe	Yes	Symptomatic	Died 15 mo.
15	1947	39	M	Chest pain	4	Mediastinal mass	P-III	Neg.	Thoracotomy; autopsy	Right upper lobe	Yes	Thoracotomy; inoperable	Died 6 mo.
16	1947	62	M	Chest pain	1	Solitary mass	P-V	Neg.	Aspiration biopsy; thoracotomy	Right upper lobe	No	Pneumonectomy	Alive and well 26 mo. postoperatively
17	1947	58	F	Chest pain, wheezing	1	Solitary mass	P-V	Neg.	Thoracotomy	Left upper lobe	Yes	Pneumonectomy	Died 9 mo. postoperatively
18	1948	50	M	Virus pneumonia	3	Multiple nodules	P-V	Neg.	Thoracotomy; sputum cytology	Right lower lobe	Yes	Pneumonectomy	Died 6 mo. postoperatively
19	1948	59	M	Dyspnea	12	Patchy density	P-V	N	Autopsy	Left lower lobe	Yes	Symptomatic	Died 12 mo.
20	1949	59	M	None	..	Solitary mass	N	Neg.	Thoracotomy; aspiration biopsy	Right lower lobe	Yes	Segmental resection plus radiation	Alive 8 mo. postoperatively, with disease
21	1949	43	F	None	..	Solitary mass	N	Neg.	Thoracotomy	Left upper lobe	Yes	Pneumonectomy	Alive 8 mo. postoperatively, without disease
22	1949	57	M	Chest pain	3	Pleural effusion	P-I Tb N	Pos.	Bronchoscopy; thoracotomy	Entire left lung	Yes	Pneumonectomy	Died 4 days postoperatively
23	1949	51	M	Chest pain	5	Pleural effusion	N	Neg.	Pleural biopsy	Entire left lung	Yes	X-Ray	Alive 7 mo.
24	1949	51	M	Cough	6	Hilar mass; patchy density	P-V	Neg.	Sputum cytology; pneumonectomy	Right hilar area	Yes	Pneumonectomy	Alive 5 mo. postoperatively
25	1949	66	M	Cough	9	Hilar mass; atelectasis	P-II	N	Biopsy supraclavicular node	Right upper lobe	Yes	X-Ray	Alive 3 mo. after treatment
26	1949	50	M	Dyspnea	5	Solitary mass	P-III	Neg.	Thoracotomy	Left upper lobe	No	Lobectomy	Alive 2 mo. postoperatively
27	1949	52	F	Dyspnea	?	Solitary mass	P-III	N	Thoracotomy; aspiration biopsy	Right upper lobe	No	Pneumonectomy	Alive 6 mo. postoperatively
28	1949	62	M	Chest pain	1	Infiltrative mass	P-I	N	Supraclavicular lymph node biopsy	Left lung	Yes	X-Ray	Died 5 mo. after treatment
29	1949	55	F	None	..	Solitary mass	P-IV	Neg.	Sputum cytology; pneumonectomy	Right upper lobe	No	Pneumonectomy	Alive 3 mo. postoperatively
30	1949	41	M	Cough	12	Hilar mass	P-IV	Neg.	Sputum cytology; thoracotomy	Right hilar area	Yes	Thoracotomy; X-Ray	Alive 3 mo.
31	1949	71	M	Chest pain	3	Multiple nodules	P-IV	Pos.	Bronchoscopic; lymph node biopsies	Diffuse, both lungs	Yes	Symptomatic	Died 4 mo.
32	1949	56	M	Cough, chest pain	1	Multiple nodules; bilateral	P-IV	Neg.	Aspiration biopsy of lung mass	Diffuse, both lungs	Yes	X-Ray	Alive after 3 mo.
33	1949	49	F	None	..	Solitary mass	P-III	Neg.	Thoracotomy	Right upper lobe	No	Lobectomy	Alive 3 mo., without disease

* P-I to V: Papanicolaou classification of smears; Tb N.: negative for tuberculosis; N: not examined.

same lung, to the opposite lung or to peribronchial or hilar nodes. In five of the nine patients who were subjected to pneumonectomy, lymph nodes removed with the lung contained metastatic carcinoma. Among 10 patients in whom a solitary lung nodule was the only clinical evidence of cancer, metastases were found in regional nodes in four instances.

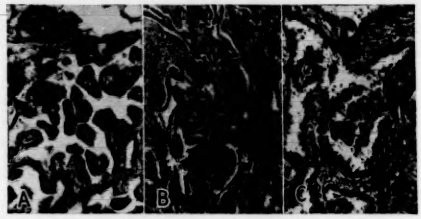

Fig. 7.—*A*, photomicrograph of tissue removed from patient (case 21), showing papillary formation in terminal bronchiolar carcinoma. *B*, an adjacent area from the specimen, showing fibrosis. *C*, photomicrograph of an area of terminal bronchiolar carcinoma (case 21), showing desquamated débris in the lumen.

Microscopic Appearance.—The microscopic anatomy of terminal bronchiolar carcinoma shows the distinguishing characteristics of the disease, which are unlike those seen in the commoner type of bronchogenic carcinoma. The alveolar spaces are lined by cuboidal or columnar nonciliated epithelium in several layers or in papillary formation. The alveoli may be distended and completely filled with proliferating epithelium. Single cells or clusters containing large multinucleated giant cells may be found lying free in the alveolar spaces. These are the same type of cells that Papanicolaou describes as characteristic of terminal bronchiolar carcinoma as evidenced in cytological studies of the sputum. The individual cells have varying degrees of pleomorphism. The nuclei are hypochromatic, rounded, vesicular or irregular in outline. Mitosis is not common. Among our cases the cytoplasm was acidophilic and relatively abundant. Signet-ring cells, so characteristic of adenocarcinomas of gastrointestinal origin, were found in one-half the cases. The vacuoles of the signet-ring cells contained mucin and were indistinguishable microscopically from those seen elsewhere in carcinomas arising in mucus-producing glands.

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COMMENT

The microscopic appearance of terminal bronchiolar carcinoma, together with the failure to demonstrate origin from the primary or secondary bronchi, supports the view that this type of cancer arises from the lining cells of the terminal bronchioles or alveoli. The nature of the lining epithelium of the alveoli is still a controversial subject, as evidenced by the discussions in recent papers.[5] Current opinion appears to favor Miller's [5] thesis of a continuous lining epithelium of the alveoli. Observations on the type of changes seen in the alveolar lining in bronchiectasis and other chronic pulmonary infections support this view. Herbut,[6] Ikeda,[7] and Bonne [8] believe that terminal bronchiolar carcinoma originates in the basal cells of the bronchioles, which proliferate and extend peripherally along the septa. Others [9] contend that the alveolar lining cells are mesenchymal in origin; however, sufficiently definite evidence in favor of this hypothesis appears to be lacking. From a practical standpoint, this problem is chiefly of academic interest, for these neoplasms are clinically and anatomically similar to other carcinomas of epithelial origin.

Anatomically, there is a close resemblance between terminal bronchiolar carcinoma and pulmonary adenomatosis. The latter is characterized by a tall columnar epithelium, paucity of mitotic figures, and absence of stromal invasion. Ewing [10] discusses pulmonary adenomatosis as an entity. However, a search of the files in the laboratories of Memorial Hospital fails to yield a single case of true, obviously "benign," pulmonary adenomatosis.

In laboratory animals, the carcinogenic effect of urethan, dibenzanthracene, and other carcinogens is well known. These carcinogens, whether given intraperitoneally, intratracheally or subcutaneously, caused the development of multiple lung tumors in 100% of susceptible mice within four months.[11] Many authors report the same histological picture in both the spontaneous and the induced tumors. They describe the tumor as an

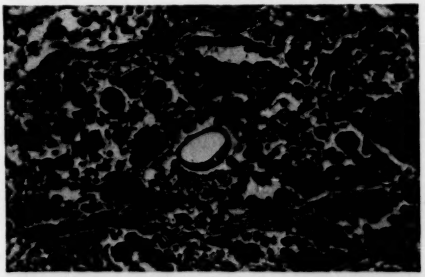

Fig. 8 (case 18).—Photomicrograph of tissue removed from the right lung of patient, showing characteristic signet-ring cells.

adenomatous tumor of alveolar cell origin, invading the lung and metastasizing to the surrounding lymph nodes. These tumors have histological characteristics similar to those of the neoplasm described in this article.

An infectious disease of similar histological appearance, occurring in sheep and in other animals, is known

as jaagsiekte (driving sickness) but is also known by various other names, such as epizootic adenomatosis, and infectious adenomatosis. It has been reported as closely resembling terminal bronchiolar carcinoma. This disease is believed to be caused by a virus that can readily be transmitted to healthy sheep when they are housed with diseased animals. Dungal [12] and his associates report one instance of successful transmission of the disease by an intrapulmonary injection of a tissue suspension. Efforts to isolate a virus or other specific agents have been unsuccessful. The histological characteristics of jaagsiekte consist of epithelial proliferations forming papillary intra-alveolar masses, which are noninvasive, singularly preserving the alveolar septa. Aynaud [13] has reported an instance of metastases in lymph nodes and subcutaneous tissues in jaagsiekte. De Kock [14] has suggested that jaagsiekte may actually be a true neoplastic disease. However, more proof is required before this hypothesis can be accepted.

SUMMARY

A clinical and histological study of 33 patients with terminal bronchiolar carcinoma of the lung is presented. In the majority of these cases the disease ran a rapid clinical course. Chest pain and cough were the commonest presenting symptoms. In 15% the disease was asymptomatic and was discovered by routine roentgenographic studies of the chest. A positive cytological diagnosis of cancer was made in nine instances. The distinguishing feature of terminal bronchiolar carcinoma of the lung is seen in its gross and microscopic appearance. Grossly, it has been divided into two forms—nodular (70% of this series) and diffuse (30% of this series). Cytologically, the two forms are identical. The only effective treatment is surgical excision. Two of the patients in whom surgical intervention was attempted prior to 1945 are alive and well; one had a lobectomy and one a simple excision of the mass. Both were in the early stage, in which a limited procedure was sufficient to eradicate the disease. Nine patients with more extensive disease required pneumonectomy. Four are dead, and five are living, six months to two years after operation. Another means of treatment that requires more study and trial is a combination of surgery and irradiation; in this procedure the primary bulk of diseased tissue is excised, and interstitial radon in the form of gold seeds is placed in the remaining inoperable cancer. External irradiation can then be more accurately directed to the well marked residual cancer. The relation between this disease entity and so-called pulmonary adenomatosis, and jaagsiekte disease, is discussed.

340 East 72nd St.

12. Dungal, N.; Gislason, G., and Taylor, E. L.: Epizootic Adenomatosis in the Lungs of Sheep: Comparisons with Jaagsiekte, Verminous Pneumonia and Progressive Pneumonia, J. Comp. Path. & Therap. **51**: 46-68, 1938.

13. Aynaud, M.; Peyron, and Falchetti: Sur le cancer du mouton chez le mouton et ses liens étiologiques avec les lésions parasitaires et infectieuses, Compt. rend. Acad. Sc. **195**: 342-344, 1932.

14. de Kock, G.: Are the Lesions of Jaagsiekte in Sheep of the Nature of Neoplasm? Annual Report Director Veterinarian Service (Sect. 5-9) **2**: 611-641, 1929.

INTESTINAL VOLVULUS PRECIPITATED BY LEAD POISONING

REPORT OF FIVE CASES

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Our purpose is to present observations supporting our belief that intestinal volvulus may be precipitated by plumbism, a sequence of events unmentioned in the literature as far as we can determine.

It is well known that in some world areas, such as the Baltic region, volvulus may be a major cause of intestinal obstruction, reaching incidences as high as 50% of all obstructions.[1] Among the natives of the highlands of Peru as seen at this hospital,[2] volvuli also cause about 50% of all obstructions seen. The majority of these are of the sigmoid colon.

We have observed repeatedly at autopsies and at abdominal operations that the natives of this area generally possess a long, redundant, mobile megasigmoid, usually with a narrow pedicle-like mesosigmoid predisposed to twist. Of the factors mentioned in the literature as being of import in the development of such anatomically long sigmoids, the two factors that stand out most here are distinctly increased dietary roughage and congenital development. A third factor, the elevated altitude, conceivably may play a role. It has been observed by us and others that persons living at this (12,200 ft.) and higher altitudes often experience "bloating," flatulence, anorexia, abdominal discomfort, and, often, episodes of diarrhea without ascribable cause, all probably representing manifestations of disturbed gastrointestinal function related to environmental hypoxia, because these symptoms disappear on return to sea level.[3]

Of the five cases to be reported, four volvuli involved the sigmoid and one, the small bowel. All the patients had worked in the lead plant eight months to seven years, and at the time of hospitalization they showed pronounced evidence of lead absorption, as well as prior symptoms consistent with gastrointestinal plumbism merging into those of volvulus.

It seems generally agreed that during an episode of lead poisoning of the gastrointestinal type, there is an

Chief Surgeon (Dr. Berger) and Chief Physician (Dr. Lundberg) of the Cerro de Pasco Copper Corporation.

1. (*a*) Haymond, H. E.: Massive Resection of the Small Intestine: An Analysis of 257 Collected Cases, Surg., Gynec. & Obst. **61**: 693-705 (Nov.) 1935. (*b*) Perlmann, cited by Probstein, J. G., and Senturia, H. R.: Volvulus of the Sigmoid Colon, Surg., Gynec. & Obst. **77**: 669-672 (Dec.) 1943. (*c*) Campbell, D. A., and Smith, R. G.: The Diagnosis and Treatment of Volvulus of the Sigmoid Colon, S. Clin. North America **30**: 603-611 (April) 1950.

2. Chulec General Hospital is the central diagnostic and treatment center located at La Oroya, Peru, at an altitude of 12,200 feet. The cases in this report were in lead workers from the smelter located at the same altitude.

3. Crane, H. L.: Soroche, An. Fac. de med., Lima 306-309 (June) 1928. Monge, M. C.: Andean Sickness: Symptomatology, Evolution and Treatment, ibid. 128-150 (June) 1928.

intestinal turmoil consisting of uncoordinated muscular spasms of the intestinal tract, giving rise to the colic.[4] Lead poisoning can closely mimic intestinal obstruction with colicky pain, nausea, vomiting, obstipation, and even abdominal tenderness. Distention however is not described as a prominent feature in pure lead poisoning, few instances of it being cited in the literature.[5] However, we have observed distention in several instances of uncomplicated lead colic with various grades of colonic and small bowel distention discernible both on physical and radiographic examination. Intravenous administration of calcium is of great help in the differential diagnosis by relief of the pain of pure plumbism, the symptoms of a superimposed organic obstruction persisting.[6]

It is our belief that, as observed in this population group (persons with these anatomically long sigmoids described above), the effects of plumbism may precipitate a volvulus. In one case following (case 5), the small bowel was involved, and there was no anatomical lesion at operation to account for volvulus.

These cases are emergencies. If brief conservative measures do not release the volvulus, one must immediately perform an operation.

REPORT OF CASES

Case 1.—G. Y. G., a Peruvian native, 54, who had worked in the lead smelter for seven years, was admitted with generalized crampy abdominal pain of six hours' duration without nausea and vomiting, but preceded by constipation for several days. He had experienced one previous attack of gastrointestinal plumbism, which had responded to the usual treatment (intravenous administration of calcium). Examination disclosed pallor and a definite lead line of the gums. The abdomen was somewhat distended, quiet, and not tender. A plain radiograph disclosed rather pronounced distention of the colon. The hemoglobin was 16 Gm. per 100 cc.; the erythrocytes numbered 4,260,000 per cu. mm.[7] There were numerous stipple cells in the blood smear.

He was treated with meperidine (demerol®) hydrochloride, calcium intravenously, and enemas with neostigmine (prostigmin®) bromide, with partial relief of pain, and passed noticeable amounts of gas. Despite this, during the ensuing six hours, his distention increased and his general condition deteriorated. Reevaluation pointed to probable sigmoid volvulus. Major surgical intervention was judged out of the question because of his poor condition, and cecostomy alone was done with the hope that transient benefits from proximal decompression along with interim supportive measures would permit more radical surgical treatment. However, such benefits never accrued, and the patient died two days later with evidence of peritonitis and uremia. Autopsy confirmed volvulus and gangrene of the sigmoid with rupture of the involved loop and peritonitis.

On the basis of this unfortunate experience, our first encounter with combined plumbism and volvulus, we decided to increase our index of suspicion for associated volvulus in natives with evidence of lead absorption and adopt a more radical approach, because the treatment of lead poisoning and volvulus is antithetical. While pure plumbism is treated with anodynes, calcium, enemas, and bowel stimulants, sigmoid volvulus that does not readily reduce with brief conservative means is a surgical emergency.[8]

Campbell and Smith [1c] have since warned against the inadequacy of cecostomy alone in sigmoid volvulus, as used in this case and illustrated as well in other literature; with this view, we heartily agree.

Case 2.—P. S. R., 26, a Peruvian native who had worked seven years in the lead furnaces was admitted with a history of colicky abdominal pain for 11 days. For three days there had been nausea and anorexia but no vomiting. He had noted progressive muscular weakness and cramps in the extremities, but his bowels had moved daily. Blood loss from the usual avenues was denied. Examination disclosed pallor of the skin and mucous membranes. He was suffering from spasmodic abdominal pain. There was a definite lead line along the incisors. The abdomen was soft, flat, and without muscle spasm or localizing signs of any kind. There was weakness of extension at both wrists, and the strength of grip as tested with the dynamometer was distinctly reduced. The porphyrin test showed dark red fluorescence.[9] The hemoglobin was 13.6 Gm. per 100 cc., leukocytes 6,600 with 66% polymorphonuclear leukocytes. Numerous erythrocytes showed basophilic stippling. The urine showed 2 + albumin. The icterus index was 15. The blood Kahn test was normal. The diagnosis was plumbism of the gastrointestinal type, and the patient was accordingly treated with calcium intravenously, vitamins, meperidine hydrochloride, atropine, and enemas. There appeared to be improvement during the next two days, but during the following three days he increasingly complained of colicky epigastric pain. Reexamination disclosed a soft abdomen with slight tympany and tenderness in the epigastrium. There was no rebound tenderness or muscle spasm, tachycardia, or fever. A plain radiograph of the abdomen showed a distended colonic loop with fluid levels, and a barium enema indicated changes consistent with sigmoid volvulus (fig. 1).

Exploratory laparotomy was carried out immediately, the diagnosis being sigmoid volvulus. When the peritoneum was opened, odorless straw-colored fluid escaped, and hugely distended colonic, loops were present. The colon was decompressed using Carrington Williams' maneuver, this being productive of large quantities of brown fluid and gas.[10] The sigmoid was twisted 360 degrees in a clockwise direction as viewed from the position of one facing the abdomen. It was a paddle-shaped loop 3 ft. (91.44 cm.) in length. This loop was resected, and immediate end-to-end anastomosis carried out with the use of a closed technique with the Furniss clamp. Proximal decompression was carried out through a tube cecostomy. The postoperative course was uneventful except for a small wound abscess, which was promptly drained and healed. When the bowels were moving normally, the cecostomy tube was removed on the 14th postoperative day, the fistula promptly closing (fig. 2). Antilead treatment was continued postoperatively. Basophile aggregation count was not performed until three weeks after admission, at which time it was 1.8%. The result of the porphyrin test at this time was faintly rose.

This case shows the development of volvulus while therapy was being given for plumbism, the abdominal symptoms increasing under calcium treatment. A proximal vent, established at the time of an anastomosis done on the unprepared colon, permits immediate, continued decompression, early cleansing of the colon by irrigation, and the introduction of succinylsulfathiazole or other agents as accessory safeguards against breakdown and infection at the anastomotic site. In cases of

4. McNally, W. D.: Toxicology, Chicago, Industrial Medicine, 1937. Osler, W.: The Principles and Practice of Medicine, ed. 7, New York, D. Appleton and Company, 1909. Meakins, J. C.: The Practice of Medicine, St. Louis, C. V. Mosby Company, 1936. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941. Cushny, A. R.; Edmunds, C. W., and Gunn, J. A.: Pharmacology and Therapeutics, ed. 12, Philadelphia, Lea & Febiger, 1940. Christian, H. A.: The Principles and Practice of Medicine, ed. 15, New York, D. Appleton-Century Company, 1944.

5. Pickett, Nachman, and Levitt, cited by McNally, W. D.: Toxicology, Chicago, Industrial Medicine, 1937.

6. Belknap, E. L.: Differential Diagnosis of Lead Poisoning, J. A. M. A. **139**: 818-823 (March 26) 1949.

7. It must be remembered that at this altitude where polycythemia is the rule, these and subsequent figures for blood values represent a severer grade of anemia than they would indicate at sea level.

8. Bruusgaard, C.: Volvulus of the Sigmoid Colon and Its Treatment, Surgery **22**: 466-469 (Sept.) 1947; Internat. Abstr. Surg. **86**: 259-260 (March) 1948.

9. Harrold, G. G.: Urinary Porphyrins in Lead Poisoning, in Proceedings of the Lead Hygiene Conference, New York, Lead Industries Association, 1948, pp. 129-133. Waldman, R. K., and Seidman, R. M.: Reliability of the Urinary Porphyrin Test for Lead Absorption, Arch. Indust. Hyg. **1**: 290-295 (March) 1950. Maloof, C. C.: Role of Porphyrins in Occupational Diseases, ibid. **1**: 296-307 (March) 1950.

10. Williams, C., and Williams, C., Jr.: Surgical Aspiration of the Bowel in Advanced Obstruction, Ann. Surg. **131**: 846-852 (June) 1950.

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plumbism in which the lead may continue to act on the bowel postoperatively with increased ileus and dyskinesia because of its action on the musculature, cecostomy is an additional protective measure providing decompression. The fistula closes promptly if the anastomosis is not stenotic.

CASE 3.—M. A. de la C., 27, a Peruvian native laborer at the lead furnaces for 13 months, was admitted with diffuse abdominal colicky pain for a period of eight days, worse for the preceding three days. This was accompanied by vomiting, progressive constipation, and no bowel movements for two days. The symptoms had failed to abate with two days' treatment with calcium intravenously in the outpatient clinic. The patient was afebrile. There was a definite lead line along the pyorrheic lower central incisors. Wrist extension and dynamometer grip were weak. The abdomen was somewhat distended without spasm or rigidity, and generally tender to pressure but without rebound tenderness. He complained of cramps in the extremities. Laboratory studies revealed pronounced basophilic stippling, a mild leucocytosis, urinary albumin of 1 +, and a normal blood Kahn test. The result of the urinary porphyrin test was deep rose. A plain radiograph of the abdomen suggested sigmoid volvulus, and this was confirmed by barium study (fig. 3).

Immediate exploratory laparotomy revealed beefy colored fluid and a huge, obstructed, redundant sigmoid twisted 360 degrees in a clockwise direction about a narrowed mesosigmoidal pedicle. Carrington Williams' decompression and immediate resection by open end-to-end anastomosis were carried out, with removal of the 2½ ft. (76.20 cm.) sigmoid. A proximal vent was established by tube cecostomy. The postoperative course was uneventful, the cecostomy tube being removed on the 12th postoperative day, at which time the bowel movements were normal. Barium enema 26 days later showed a normal sigmoidal course (fig. 4). Basophile aggregation count could not be done until the

Fig. 1 (Case 2).—Note the huge sigmoid. As determined at operation, the barium column stopped abruptly in the lower segment of the twisted sigmoid at the distal point of obstruction. The proximal colon is distinctly distended.

19th postoperative day, at which time it was 1.2%, and the result of the porphyrin test was faintly rose. Antilead treatment was continued postoperatively, as well as penicillin and streptomycin therapy.

This case, similar to the one preceding, was handled radically with good success, and we have done immediate resections on volvuli of the sigmoid not involving lead poisoning with equally good results. It is well known that simple detorsion, which may have to be done at times, is not the best mode of surgical treatment of sigmoid volvulus because of the high incidence of recurrence.[11] Baronofsky has reported successful cases of immediate resection on the obstructed colon.[12] Pierini advocates one stage end-to-end procedures as the treatment of choice in sigmoid volvulus.[13]

Fig. 2 (Case 2).—Barium enema 25 days postoperatively showing a normal sigmoidal course with minimal redundancy and no constriction at the site of anastomosis.

CASE 4.—A Peruvian native lead smelter worker, 42, was admitted with a history of pain in the abdomen, arms, and legs of 15 days' duration. For six days prior to admission, there was a history of nausea without vomiting and obstipation. Purgatives had caused aggravation of abdominal pain without laxative effect, and 24 hours before admission, an enema was given with return of only ½ L. The patient had worked for eight months in the lead smelter, and there were no difficulties antedating the present episode. Physical examination showed a man in acute distress, who was obviously anemic. He had a well-defined lead line of the gums as viewed with a magnifier and good light. The extensors of the forearms were weak, most distinctly on the right; there was weak grip as measured by the dynamometer. The abdomen was moderately distended and tympanitic with moderate epigastric and infraumbilical tenderness elicited on palpation. No masses or spasm were present. The bowel tones were numerous, but there were no rushes, and the rectal examination was normal. Laboratory data revealed hemoglobin of 14 Gm. and leucocytes 6,000 with a normal differential. The blood smear showed punctate basophilic stippling. The urine showed 2 + albumin and the result of the urine test for coproporphyrins was positive. Abdominal plain roentgenogram showed a distinctly distended

11. Griffin, W. D.; Bartron, G. R., and Meyer, K. A.: Volvulus of the Sigmoid Colon: Report of 25 Cases, Surg., Gynec. & Obst. **81**: 287-294 (Sept.) 1945.

12. Baronofsky, I. D.: Primary Resection and Aseptic End-to-End Anastomosis for Acute or Subacute Large Bowel Obstructions, Surgery **27**: 664-672 (May) 1950.

13. Pierini, A.: Volvulus of the Sigmoid Loop, Dia méd. **21**: 526 (1949); Internat. Abstr. Surg. **89**: 559 (Dec.) 1949.

proximal large bowel, which was gas-filled, and the barium enema showed a redundant sigmoid colon, the column stopping abruptly in the left colon.

The complaints decreased after the barium enema, and it was felt that this procedure had untwisted an incompletely twisted sigmoid (less than 360 degrees). He responded to intravenous administration of calcium, vitamins, and repeated enemas. For the first two or three days, enemas were productive of little gas and feces, but because improvement was gradual, if not dramatic, and the clinical condition of the patient was good, immediate surgical intervention was not deemed necessary. On the third hospital day, the results of enemas were excellent, and thereafter the bowels functioned normally with and without the aid of purgatives. Elective resection has not yet been recommended, this patient being under continued observation and ambulatory antilead treatment.

CASE 5.—P. E. C., a Peruvian native laborer, 20, in the lead plant for two years was admitted with a chief complaint of crampy abdominal pain and obstipation for five days. He had recently noted anorexia and weakness, but there had been no nausea or vomiting, or peripheral cramps. There had been no previous episodes. Examination disclosed a fairly well-developed and fairly well-nourished man with pallor of the mucous membranes and a lead line of the gums. There was no fever; the pulse rate was 100. The abdomen was moderately distended and tympanitic with some prominence and tenderness in the epigastric region. There was no muscle spasm or rebound. The grip was weak as measured with the dynamometer, but extension was not discernibly weakened. Laboratory findings included a positive result in the urinary porphyrin test, and the blood smear showed basophilic stippling. Hemoglobin was 13.6 Gm. A plain radiograph of the abdomen showed pronounced gaseous distention of the colon, as well as multiple loops of distended small bowel

Fig. 3 (Case 3).—Barium enema showing greatly elongated sigmoid, the barium column stopping in the region normally occupied by the splenic flexure, but in actuality this represents only the distal half of the obstructed sigmoid. Note the hugely distended proximal colon.

with fluid levels in some, these being in the upper abdomen. A barium enema ruled out sigmoid volvulus, but because of the high location of the cecal shadow, an ileocecal volvulus was suspected. In view of these observations and the failure of the symptoms to abate with intravenous administration of calcium, it was felt that surgical exploration was indicated.

Laparotomy revealed an excess of clear peritoneal fluid. The small bowel mesentery was twisted clockwise 360 degrees, the distal half of the small bowel being collapsed, while the proximal half was dilated, edematous, and distended with liquid content. Except for scattered petechial hemorrhages, there was no significant impairment of the circulation either of small bowel or its mesentery. There were no congenital abnormalities located; the cecum was anchored higher than usual, and the large redundant sigmoid was not twisted. Simple detorsion was carried out, and calcium therapy was continued postoperatively. Recovery was uneventful.

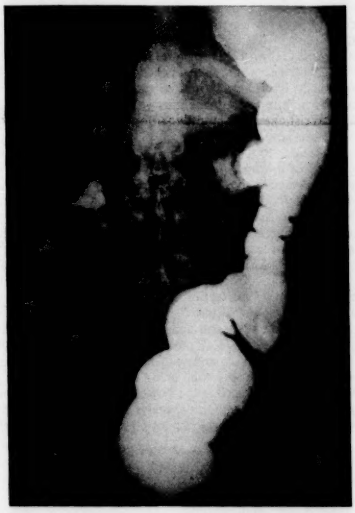

Fig. 4 (Case 3).—Barium enema 26 days later showing a normal sigmoidal course without undue redundancy, and with slight but asymptomatic narrowing at the site of primary anastomosis.

In this instance it would appear that because of the action of lead on the bowel, volvulus may sometimes occur in the absence of contributory anatomical abnormalities.

SUMMARY AND CONCLUSIONS

Five cases of volvuli associated with lead poisoning, four involving the sigmoid and one the small bowel, are presented. There was one fatality through our failure to recognize early that both volvulus and lead poisoning were present; the other four patients recovered. Two cases required prompt surgical intervention for complete sigmoid obstruction, and immediate resection was successful. The small bowel case required only detorsion. One other case underwent spontaneous detorsion during a diagnostic barium enema. The role of plumbism in the precipitation of volvulus is discussed. In all the cases presented, symptoms consistent with those of gastrointestinal plumbism preceded by a matter of days the more acute symptoms heralding the onset of volvulus. To us, this temporal relation between these two diseases is so clear that we feel it is justifiable to relate them causally and to conclude that intestinal volvulus may be precipitated by lead poisoning, especially in those instances in which a megasigmoid or other predisposing factor exists.

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PHENACEMIDE IN TREATMENT OF EPILEPSY

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The purpose of this paper is to classify and tabulate the extensive clinical reports on the use of phenacemide (phenurone®) in the treatment of epileptic seizures, in order to attain a clearer picture of the uses and limitations of the drug which might otherwise not be available and to acquaint physicians with an anticonvulsant drug which, when used alone or in combination with other anticonvulsants, is capable of relieving certain patients of seizures which are not affected by other antiepileptic drugs known at present. Since this drug is not without toxic potentialities, physicians who use it should be thoroughly acquainted with the undesirable side effects which may occur and the precautions to be observed as well as with its efficacy.

This paper is not intended to discourage or interfere with subsequent publications by individual investigators. On the contrary, it is hoped that those who have had experience in the use of phenacemide, particularly those using it in a relatively large series of cases, will publish their results.

Phenacemide, known chemically as phenacetylcarbamide, was synthesized by Spielman,[1] and its anticonvulsant properties investigated by Richards and Everett.[2] It is a drug of low toxicity when given orally to animals. It possesses slight sedative action and remarkable anticonvulsant activity. Doses of 400 mg. per kilogram produce slight ataxia in mice and cats. In all animals heart rate and respiration were not impaired. Rats kept on diets containing 0.25, 0.5, and 1.0% phenacemide for 24 mo. showed no significant changes in growth rate, blood status, or urine. Dogs on daily doses of 100, 200, 400, and 600 mg. per kilogram from six to 18 mo. had normal values for blood and kidney function. Liver-function tests remained normal. Repeated bone-marrow smears showed normal marrow elements. Cats do not tolerate phenacemide as well as do dogs and rodents. Phenacemide is highly effective against supramaximal electroshock seizures and pentylenetetrazol convulsions in mice and rabbits at doses of 300 mg. per kilogram orally, the effect lasting for three to four hours. In a new test,[3] which produces focal seizures of a psychomotor type in animals, phenacemide was more effective than other commonly used anticonvulsants. Studies in mice have shown a synergistic anticonvulsant action between phenacemide and mesantoin® (3-methyl-5,5-phenylethylhydantoin), phenacemide and phenobarbital, and phenacemide and trimethadione (tridione®).

THERAPEUTIC RESULTS

In the majority of cases, phenacemide has been used in the treatment of epilepsy when other anticonvulsants have been tried and have failed to control completely or to reduce the frequency of the seizures. This method of evaluation constitutes a severe test. In a total of 1,539 patients, approximately 65% have shown improvement when phenacemide was given alone or in combination with other anticonvulsants, such as phenobarbital, diphenylhydantoin (dilantin®), and mesantoin.® In 539, or 35% of the total, the seizures have been completely controlled or reduced in frequency 75% or more. Thirty-five per cent of the phenacemide treatments were classed as failures, either because phenacemide therapy did not bring about improvement in the patient's condition or because it became necessary to discontinue the drug when side effects occurred.

When types of seizures (Table 1) were considered individually, whether they occurred alone or in combination with other types, it was found that their frequency of occurrence was reduced in 68% of the patients. Sixty-three per cent of the patients with petit mal, 70% of the patients with grand mal and 68% of the patients with psychomotor seizures were benefited.

TABLE 1.—*Results of Phenacemide Therapy in Relation to Types of Seizures*

Type Seizure	Total No. of Seizures	Greatly* Improved Patients		Improved† Patients		Total Improved Patients		Unaffected Patients	
		No.	%	No.	%	No.	%	No.	%
Psychomotor...	448	163	36	144	32	307	68	141	32
Petit mal.....	455	151	33	138	30	289	63	166	37
Grand mal.....	659	258	39	203	31	461	70	198	30
Mixed‡	593	163	27	187	32	350	59	243	41
Total.....	1,562	572	37	485	31	1,057	68	505	32

* 75% reduction in frequency of seizures to complete control.
† 35% to 75% reduction in frequency of seizures.
‡ Not included in total.

Fifty-nine per cent of the patients with mixed types of seizures experienced definite reduction in the number of seizures.

Five hundred and eighty of the total number of patients suffered from only one type of epileptic seizure (Table 2). One hundred and eighty-six had petit mal, and of these 54, or approximately 29%, showed a 75% reduction in the number of seizures or complete control. One hundred and eight, or 58%, were improved. There were 273 patients with grand mal of whom only 33% showed improvement. Seventy per cent of the patients with psychomotor epilepsy were improved. Approximately the same percentage were found to be benefited whether the psychomotor epilepsy occurred alone or in combination with other types of seizures. From an analysis of these figures, which also include data from

Drs. R. K. Richards and G. M. Everett of the Department of Pharmacology, Abbott Laboratories, cooperated in the preparation of this paper.
From the Department of Clinical Investigation, Abbott Laboratories (Dr. Tyler), and the Medical Division, Food and Drug Administration, Federal Security Agency (Dr. King).

1. Spielman, M. A.; Geiszler, A. O., and Close, W. J.: Anticonvulsant Drugs II. Some Acetylureas, J. Am. Chem. Soc. **70**: 4149 (Dec.) 1948.
2. Everett, G. M.: Pharmacological Studies of Phenacetylurea (Phenurone), An Anticonvulsant Drug, Federation Proc. **8**, Part I: 289, 1939. Richards, R. K., and Everett, G. M.: Laboratory Records, Department of Pharmacology, Abbott Laboratories, unpublished data.
3. Everett, G. M., and Toman, J. E. P.: Experimental "Psychomotor" Seizures and Antiepileptic Drugs, Federation Proc. **10**: 293 (March) 1951.

published reports,[4] it would seem that phenacemide is most effective in controlling psychomotor seizures. Disturbing personality changes are most likely to occur in patients with this type of seizure. It is suggested that phenacemide be used cautiously in the treatment of patients with psychomotor epilepsy who have previously exhibited marked personality problems. The incidence of control of the grand mal seizures was greatest when grand mal occurred in combination with either petit mal or psychomotor epilepsy. The drug was less effective in the treatment of grand mal alone.

TABLE 2.—*Patients in Whom Only One Type of Seizure Occurred*

Type Seizure	Total No. of Patients	Greatly* Improved Patients No.	%	Improved† Patients No.	%	Total Improved Patients No.	%	Unimproved Patients No.	%
Psychomotor	121	62	51	24	19	86	70	35	30
Petit mal	186	54	29	54	29	108	58	78	42
Grand mal	273	62	23	28	10	90	33	183	67
Total patients	580	178	31	106	18	284	49	296	51

* 75% reduction in frequency of seizures to complete control.
† 35% to 75% reduction in frequency of seizures.

Studies with animals have shown that phenacemide acts synergistically with other anticonvulsants. An attempt was made to determine whether this is also true with humans. Reports on 596 patients enabled us to determine how many of these were treated with phenacemide alone and how many with a combination of anticonvulsants. Of the 596, 290 received only phenacemide. Because of the presence of combined seizures in some of these, a total of 384 seizures or seizure combinations were treated. Table 3 shows that phenacemide alone is effective in controlling or reducing seizures and is also effective when used in combination with other anticonvulsants.

Phenacemide controls or markedly reduces the frequency of seizures to about an equal extent in adults and children.[4b] One report [6] on 35 children showed that eight (23%) were entirely free of attacks for three to 17 mo. Fifteen (43%) were improved, and 12 were not benefited. Four of these patients had a morbilliform rash after use of the drug. Two of these were able to take the drug without recurrence of the rash after it had been discontinued for a short interval. The incidence of more serious side effects would seem to be lower in children than adults. This is particularly true of the occurrence of severe emotional or psychological reactions.[7a] In many cases where children were considered behavior problems before institution of phenacemide therapy, their behavior improved, and many were reported able to get along better in school and receive better grades.

TABLE 3.—*Results of Treatment with Phenacemide Alone and in Combination with Other Anticonvulsant Drugs*

Treatment	Total Seizures	Grand Mal: Total Patients	Grand Mal: Patients Greatly* Improved (%)	Grand Mal: Patients Improved † (%)	Grand Mal: Total Patients Improved (%)	Grand Mal: Patients Unaffected (%)	Petit Mal: Total Patients	Petit Mal: Patients Greatly* Improved (%)	Petit Mal: Patients Improved † (%)	Petit Mal: Total Patients Improved (%)	Petit Mal: Patients Unaffected (%)	Psychomotor: Total Patients	Psychomotor: Patients Greatly* Improved (%)	Psychomotor: Patients Improved † (%)	Psychomotor: Total Patients Improved (%)	Psychomotor: Patients Unaffected (%)	Mixed‡: Total Patients	Mixed‡: Patients Greatly* Improved (%)	Mixed‡: Patients Improved † (%)	Mixed‡: Total Patients Improved (%)	Mixed‡: Patients Unaffected (%)
Phenacemide only	384	179	48	28	76	24	107	45	26	71	29	98	59	21	80	20	75	55	29	84	16
Diphenylhydantoin and phenacemide	91	42	59	26	85	15	26	62	19	81	19	23	52	44	96	4	25	60	28	88	12
Phenobarbital and phenacemide	103	54	47	24	71	29	32	25	41	66	34	17	59	18	77	23	29	28	48	76	24
Phenobarbital, diphenylhydantoin, and phenacemide	57	26	43	42	85	15	19	32	37	69	31	12	50	50	100	0	14	36	50	86	14
Diphenylhydantoin, mesantoin®, and phenacemide	24	14	58	21	79	21	3	66	34	100	0	7	29	29	58	42	4	50	50	100	0
Mesantoin® and phenacemide	25	12	50	25	75	25	3	66	0	66	34	10	60	30	90	10	4	50	50	100	0
Mesantoin®, phenobarbital, and phenacemide	19	7	29	14	43	57	8	63	13	76	24	4	50	0	50	50	6	68	16	84	16

* 75% reduction in frequency of seizures to complete control.
† 35% to 75% reduction in frequency of seizures.
‡ Not included in total.

The results reported by the investigators who have used phenacemide in the treatment of epileptic seizures have agreed quite well, with the exception of one group.[5] The patients treated by this group of investigators were those whose seizures were uncontrolled by established anticonvulsant therapy. Use of phenacemide in their experience, brought about a reduction in frequency of seizures in 20 out of 63 patients, or 32%.

TYPE AND INCIDENCE OF SIDE EFFECTS

The side effects most frequently seen were either favorable or unfavorable personality changes. The commonest manifestations of untoward reactions are decreased interest in surroundings, depression, suicidal tendencies, or, rarely, aggressiveness. On the other hand, in some cases of pre-existing personality disorders improvement has been noted. Personality changes have occurred in approximately 17% of all cases and have usually appeared within the first four to six weeks of phenacemide therapy. The other more serious side effects which

4. (*a*) Gibbs, F. A.; Exerett, G. M., and Richards, R. K.: Phenurone in Epilepsy, Dis. Nerv. System **10**: 47 (Feb.) 1949. (*b*) Zeifert, M.: Phenurone in Epilepsy, Dis. Nerv. System **10**: 245 (Aug.) 1949. (*c*) Livingston, S., and Kajdi, L.: Use of Phenurone in the Treatment of Epilepsy, J. Pediat. **36**: 159 (Feb.) 1950. (*d*) Little, S. C., and McBryde, R. R.: Use of Phenylacetylurea (Phenurone) in Convulsive Disorders, Am. J. M. Sc. **219**: 494 (May) 1950.

5. Carter, S.; Sciarra, D., and Merritt, H. H.: Phenylacetylurea in the Treatment of Convulsive Seizures, Dis. Nerv. System **11**: 139 (May) 1950. Carter, S., and Merritt, H. H.: Medical Therapy of Epilepsy, Journal-Lancet **70**: 103 (March) 1950.

6. Keith, H. M.: Use of Phenurone for Convulsive Disorders of Children: Preliminary Report, Proc. Staff Meet., Mayo Clin. **25**: 594 (Oct.) 1950.

7. (*a*) Davidson, D. T. Jr., and Lennox, W. G.: Phenacetylurea–Phenurone–in Epilepsy, Dis. Nerv. System **11**: 167 (June) 1950. (*b*) Levy, R. W.; Simons, D. J., and Aronson, S. M.: Fatal Hepatorenal Syndrome Associated with Phenurone Therapy, New England J. Med. **242**: 933 (June 15) 1950.

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have been encountered are evidence of liver damage and changes produced on the hemopoietic system. In addition, in the order of decreasing frequency (as shown in Table 4), gastrointestinal symptoms, rash, drowsiness, headache, and insomnia have been produced.

PERSONALITY DISTURBANCES

Information is available as to the presence or absence of personality disorders in 350 patients previous to phenacemide therapy (Table 5). There was some evidence of psychiatric disturbances in 83, or 24%, of these patients. Thirty-two, or 39%, of the 83 patients showed definite improvement after the administration of phenacemide, as contrasted with 23, or 27% whose behavior was aggravated by use of the drug. In 28 patients, previously existing personality difficulties were

TABLE 4.—*Frequency of Side Effects in 1,539 Cases*

	No. of Cases	%
Psychic changes	263	17
Hepatitis	31	2
Deaths	4	
Gastrointestinal symptoms	130	8
Anorexia	78	
Nausea and vomiting	36	
Abdominal distress	15	
Diarrhea	1	
Rash	79	5
Exfoliative dermatitis	1	
Drowsiness	58	4
Blood changes	36	2
Leukopenia	22	
Leukocytosis	6	
Low platelet count	4	
Aplastic anemia with death	2	
Granulocytopenia	2	
Headache	24	2
Abnormal urinary findings	21	1
Transient albuminuria	8	
Acetone	10	
Sugar	2	
Nephritis	1	
Insomnia	15	1
Fatigue	14	..
Fever	14	..
Dizziness	11	..
Paresthesia	5	..
Muscle pain	5	..
Weight loss	5	..
Palpitation	3	..
Pruritus	1	..

not affected. With 73% of these patients, therefore, phenacemide therapy could be continued. In 19, or 5%, of the 350 patients who had not previously exhibited personality difficulties psychic changes developed after phenacemide therapy was started. Depression developed most frequently. Other psychological manifestations reported were violence, paranoia, irritability, and suicidal tendencies.

Since administration of phenacemide has brought about an improvement in behavior in some patients, the existence of personality disorder need not be considered a contraindication to the use of the drug, but in patients with previous psychotic background there is a greater tendency for personality disturbances to develop. However, the patient should be very carefully observed, preferably hospitalized temporarily. If the disorder becomes exaggerated or new personality changes occur, use of the drug should be promptly stopped. Withdrawal and loss of general interest may indicate the onset of serious personality disturbance.

TOXIC EFFECTS ON LIVER

As shown in Table 4, there were 31 cases in which signs of liver damage were clinically observed. In 27 of these jaundice cleared when the medication was discontinued. In the other four patients hepatitis was the immediate cause of death. The role of phenacemide in producing liver damage is difficult to evaluate in two of the cases.[7] These deaths occurred during the early stage of the clinical investigation, before the possible hepatotoxic effects of phenacemide were realized. At the time of writing, there have been no reports of deaths during a period of 14 mo. This, in all probability, is due to closer supervision of the patient by the physician and to the observance of recommended precautions.

It is difficult to evaluate the reports of abnormal deviation of liver function, as shown by tests such as cephalin flocculation and thymol turbidity and flocculation. In some cases these tests have become positive, but continuation of the drug has not produced further indication of liver damage. Urine urobilinogen excretion was not significantly increased, and no retention of sulfobromophthalein (bromsulfalein®) occurred. These observations do not minimize the danger of possible liver damage but show that laboratory findings must be

TABLE 5.—*Special Study of Personality Changes*

		No.	%
Total no. of patients		350	
Patients with previous psychological disturbances		83	24
Effect of phenacemide	Personality improved	32	39
	Personality worse	23	27
	No change	28	34

correlated with sound clinical judgment in the use of the drug, which has been implicated in the production of pathological changes in the liver. Urine urobilinogen determinations should be made on all patients before phenacemide therapy is started and at frequent intervals thereafter. If the test becomes positive to a degree considered significant (1 to 20 or over), other liver-function tests should be made, preferably the sulfobromophthalein retention.

BLOOD CHANGES

Blood changes have been reported in 36 patients. Leukopenia (leukocyte count of 4,000 or less per cubic millimeter of blood) was the commonest condition observed, and it developed in 22 patients while phenacemide was being given. The leukocyte count returned to normal in 20 patients upon withdrawal of the drug. In the other two patients death, due to aplastic anemia,[8] occurred. The role of phenacemide in producing aplastic anemia is uncertain. In one patient [9] other anticonvulsant medications were used concurrently.[8a] In the second patient [8b] other antiepileptic medications had

8. (*a*) Forster, F. M., and Frankel, K.: Fatal Aplastic Anemia During Anti-Convulsant Therapy: Report of a Case During Phenurone Therapy and Following Mesantoin Therapy, Dis. Nerv. System **10**: 108 (April) 1949. (*b*) Simpson, T. W.; Wilson, E. B. Jr., and Zimmerman, S. L.: Fatal Aplastic Anemia Occurring During Anticonvulsant Therapy: Probable Idiosyncrasy to Phenurone, Ann. Int. Med. **32**: 1224 (June) 1950.

9. Forster, F. M., and Borkowski, W. J.: Paradione in Treatment of Petit Mal Epilepsy, Am. Pract. & Digest. Treat. **1**: 406 (April) 1950. Forster, F. M.: Therapy in Psychomotor Epilepsy, J. A. M. A. **145**: 211, (Jan. 27) 1951.

been given with phenacemide for a time, but they had been discontinued some weeks before the onset of toxic symptoms.

OTHER SIDE EFFECTS

Gastrointestinal symptoms were reported in 130, or 8%, of 1,539 patients (Table 4). Anorexia, nausea, and vomiting occurred most frequently. In some patients these symptoms were severe enough to require discontinuing the drug. Administration of vitamin B complex has controlled these symptoms in some patients. Rash was observed in 79, or 5%, of the patients. In most patients this indicated a real sensitivity to the drug. In a few patients a second trial with phenacemide did not produce a recurrence of the rash. Abnormal urinary findings were reported in 21 patients. In recent months there have been no reports of damaging effects on kidney function. Drowsiness has been noted in 4% of the patients, headache in 2%. Insomnia, fatigue, and dizziness have been seen less frequently. Insensitivity to pain was reported in one patient.[10]

DOSAGE

The dose of phenacemide must be individualized, based on the response of the patient. It has been observed by some investigators that side effects are less likely to develop if the dosage is gradually built up to that which will control the seizures. It is recommended that if some degree of control of seizures has been obtained with other medication such medication be continued and phenacemide added at a dosage of 0.5 gm. three times a day. The dosage of phenacemide should be increased above this starting dosage until seizures are controlled or limiting side effects develop. If it seems that the control of seizures can be maintained with use of phenacemide alone, other medication can be reduced, but if a combination of phenacemide with other drugs produces better control of seizures, or allows control to be maintained with a lower dosage of phenacemide or with less disturbing side effects, the combination should be continued as maintenance medication. It is recommended that an initial course of 0.5 gm. three times a day at meals be prescribed to adult patients. After one week an additional 0.5 gm. may be taken when the patient rises, and in the third week the dose may be increased by 0.5 gm. at bedtime. An average dose of 2 to 3 gm. per day has been adequate for most adults. If seizures continue in spite of medication and the drug is well tolerated, the dosage may be increased at a more rapid rate than that suggested above. Doses up to 5 gm. per day have been given. However, some patients obtain relief with small doses, for instance, one 0.25 gm. tablet three times a day, but will not tolerate large amounts. For children of 5 to 10 yr. approximately one-half the adult dose is recommended. Since the duration of action of the drug appears to be three to five hours, the above distribution of dosage would be optimal. The maintenance dose should be the smallest amount which will adequately control seizures.

10. Forster, F. M., and Frankel, K.: Insensitivity to Pain as a Complication of Phenurone Therapy in Epilepsy, Dis. Nerv. System **11**: 24 (Jan.) 1950.

11. Abbott, J. A., and Schwab, R. S.: Serious Side Effects of Newer Antiepileptic Drugs: Their Control and Prevention, New England J. Med. **242**: 943 (June 15) 1950.

Precautions.—For the safety of the patient the following precautions must be observed:

1. Except in carefully selected patients, phenacemide should not be administered until other accepted anticonvulsants have been tried and found ineffective in controlling epileptic seizures.

2. A careful history should be taken to determine the presence or absence of pre-existing personality disorders. Since phenacemide has brought about an improvement in behavior in many patients, the existence of personality disorder need not be considered a contraindication to the use of the drug. However, the patient should be very carefully observed. Should the disorder become exaggerated or undesirable personality changes occur, the drug should be promptly withdrawn.

3. A careful history regarding previous allergic reactions to drugs should be taken.

4. Careful clinical observation of the patient, particularly during the early months of treatment, is very important. Gastrointestinal upset, general malaise, and fever may be indicative of early liver damage or blood dyscrasia. psychological signs such as withdrawal and loss of general interest may indicate the onset of serious personality disturbance. It is recommended that the interval between examinations be not more than two weeks for the first four months and monthly thereafter.

5. The patient or his family should be advised that the use of phenacemide entails a certain risk which must be weighed against the possible benefits to be derived. The patient and his family must be instructed to watch for the occurrence of a dark urine or yellow sclera, the occurrence of a rash, or evidence of gastrointestinal upset, such as anorexia, nausea, and vomiting. In addition, the family must be instructed to look carefully for changes in the behavior of the patient. If any of these changes occur, they must be reported promptly to the physician. In some patients the gastrointestinal symptoms have yielded to treatment with vitamin B complex, which has permitted the continued use of phenacemide.

6. Complete blood counts should be made before institution of phenacemide therapy and at monthly intervals thereafter. If no abnormality occurs within 12 mo., the interval between counts may then be extended. Emphasis should be placed upon erythrocyte and leucocyte counts and the total number of polymorphonuclear cells per cubic millimeter of blood, as these are a better index of possible blood dyscrasia than the percentage of cells.

7. The patient should be carefully observed for evidence of liver damage. The urine urobilinogen test is the simplest test and can be performed in the physician's office. If this becomes positive (1 to 20 or more), other liver-function tests should be done. The sulfobromophthalein retention test is suggested. The drug should be used with caution to patients with histories of previous liver dysfunction.

8. Only enough phenacemide to last for a designated interval should be prescribed.

CONCLUSION.

The statement regarding the use of anticonvulsant drugs which appeared in a fairly recent article [11] seems entirely logical.

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An efficient drug whose side effects can be largely prevented by care should not be condemned because of a small number of serious side effects attributed to its use in the literature. Instead, an understanding and perhaps overcautious, protective regimen should be set up and meticulously followed. If this is done, side reactions tend to become fewer and fewer, and patients are not deprived of therapy they need.

Phenacemide (phenurone®) has proved to be effective in controlling or definitely reducing the frequency of seizures in a fairly large percentage of patients who have not responded to other anticonvulsant drugs. However, four deaths due to hepatitis and two due to aplastic anemia were reported prior to the initiation of controls for observing the patients. Personality changes may also develop. The drug should not be used unless other established anticonvulsants have failed to be effective. The patient or his family should be fully aware of the nature of the drug and of the side effects which may be produced. They should realize there is a certain risk which must be weighed against the possible benefits derived from its use. The physician should instruct the patient to watch for signs of toxicity and report them promptly. The patient should be seen by the physician at frequent intervals. To this end, only enough phenacemide to last for a short, designated interval should be prescribed.

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HEMOPTYSIS IN MITRAL STENOSIS

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Although the fact that mitral stenosis may cause hemoptysis long has been recognized, little emphasis apparently has been placed on its occurrence or prognostic significance. Indeed, there is a paucity of literature on this subject. Stewart,[1] in 1934, reported three cases with autopsy findings. He enumerated five situations in which blood appears in the sputum of patients suffering from mitral stenosis; namely, (1) pulmonary edema, (2) pulmonary infarction, (3) during the course of primary pneumonia, (4) paroxysmal pulmonary hemorrhage as described by Oppenheimer and Schwartz,[2] and (5) as a sign of "acute cardiac failure." More recently, Wolff and Levine [3] reported 50 cases of mitral stenosis with no selection of cases as to etiology of the hemoptysis.

In reviewing hospital records of these cases, it became apparent that there is considerable lack of understanding of this problem, especially in the absence of congestive failure. In the investigation of the symptom, bronchoscopy was carried out in two cases, in one of which the patient was put at bed rest for eight months in spite of a normal chest x-ray. Disturbed by the recent publicity regarding the early symptoms of cancer, these patients now, more than ever, demand an explanation of the cause of the hemoptysis, and the physician should be aware of the frequency of its occurrence in mitral stenosis. For these reasons a discussion of this subject seems justified.

MECHANISM

In addition to the pulmonary or lesser circulation, the lungs have a bronchial blood supply at systemic pressure which nourishes the stroma. These bronchial arteries follow each bronchus and its subdivisions, but ultimately this blood joins the pulmonary arterial blood through bronchopulmonary anastomoses. Distinct bronchial veins are found only at the hilus of the lung, the greater part of the blood of both bronchial and pulmonary arteries being returned by way of the pulmonary vein. If inflammation, thrombosis, or embolism involving smaller branches of the pulmonary artery occurs, alterations take place in this dual circulation, the bronchial arteries rapidly increase in size,[4] and a collateral circulation is established. Ferguson, Kobilak, and Deitrick,[5] in 11 autopsied cases with mitral stenosis, were able by injection methods to demonstrate dilated venous channels, in four of which cases there were innumerable wide submucosal channels running parallel to the lumina of the secondary and tertiary bronchi. They are apparently beyond the visualization of the bronchoscope. In four of the 11 cases there was a history of hemoptysis, and dilated venous channels were demonstrated in three of them; the fourth had acute hemorrhagic bronchitis, making it impossible to see these vessels. It was the opinion of these observers that the increased pressure in the pulmonary vein in the presence of mitral stenosis surpassed the pressure in the right auricle, causing a reverse flow of blood through the anastomoses with dilatation to handle the collateral flow.

Bland and Sweet,[6] who have successfully increased the collateral flow in these cases by a venous shunt between the azygos and pulmonary veins, found pressure readings from 425 to 535 mm. of water in the left auricle at the time of surgery (normal being about 100 mm.). Ferguson [5] and his group compared bleeding from these bronchial varicosities to that of hemorrhoidal or esophageal varices which, like bronchial veins, are submucosal

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1. Stewart, H. J.: The Occurrence of Hemoptysis as a Symptom of Acute Heart Failure in the Presence of Mitral Stenosis, M. Clin. North America **18**: 917, 1934.

2. Oppenheimer, B. S., and Schwartz, S. P.: Paroxysmal Pulmonary Hemorrhages, Am. Heart J. **9**: 697, 1934.

3. Wolff, L., and Levine, H. B.: Hemoptysis in Rheumatic Heart Disease, Am. Heart J. **21**: 163, 1941.

4. Rubin, E. H.: Diseases of the Chest, Philadelphia, W. B. Saunders Company, 1948, chap. 33.

5. Ferguson, F. C.; Kobilak, R. E., and Deitrick, J. E.: Varices of the Bronchial Veins as a Source of Hemoptysis in Mitral Stenosis, Am. Heart J. **28**: 445, 1944.

6. Bland, E. F., and Sweet, R. H.: A Venous Shunt for Advanced Mitral Stenosis, J. A. M. A. **140**: 1259 (Aug. 20) 1949.

shunts between large venous areas. A severe coughing spell, mild ulcerative bronchitis, or any rise in the left auricular pressure could initiate such attacks of hemoptysis. Wolff and Levine [3] suggested that sclerosis of pulmonary vessels was a necessary precursor of hemorrhage; however, two of Ferguson's four patients with hemoptysis showed no evidence of pulmonary sclerosis. Diapedesis of blood has been suggested as a mechanism but seems incredible as an explanation of large quantities of frank blood such as is seen in many cases of mitral stenosis.

MATERIAL

Records of 85 cases of mitral stenosis admitted to the Charleston General Hospital were reviewed, of which 15, or 17.7%, had a history of hemoptysis. In addition, 83 cases of mitral stenosis seen in the private practice of one of us (W. C. S.) were reviewed, of which number, 14 carried a history of hemoptysis making a combined total of 17.3%. All cases in which hemoptysis could be attributed to pneumonia or pulmonary infarction or to any other incidental cause were eliminated, as we were interested only in those cases in which the hemoptysis was consequential to a stenosed mitral valve. We found that the cases fell into three distinct groups which will be presented and discussed separately. These groups are (1) those with none to slight cardiac enlargement with no congestive failure; (2) those with moderate to great cardiac enlargement without signs of congestive failure, and (3) those with moderate to great enlargement of the heart, with congestive failure.

GROUP ONE

In Group 1, there were 10 cases, in eight of which the patients were women. The age range was from 19 to 36 years, averaging 27 years at the time of onset of hemoptysis. The length of time since onset of hemoptysis averaged 37 months, varying from one to 70 months. All patients were well when last seen.

Brief histories of three representative cases are given.

CASE 1.—Mrs. B. F. H., aged 32 years, had rheumatic fever in childhood, and was found to have mitral stenosis nine years ago. About one year before this report, she coughed up one pint (473 cc.) of blood, and since then had spit a considerable quantity of blood on three or four occasions. There had been no cough nor any wheezing. Her exercise tolerance was good, and there were no symptoms of congestive failure. Several chest x-rays, a bronchogram, and three bronchoscopic examinations were noncontributory.

Physical examination revealed the following: blood pressure 116/70; mitral stenosis with slight cardiac enlargement; sinus rhythm; no signs of congestive failure.

CASE 2.—Mrs. E. E. T., aged 23 years, had chorea at the age of 12 years. Three and one-half years before this report hemoptysis had occurred after intercourse. Recently, on two occasions, hemoptysis had followed intercourse. For two days previous to examination the patient noted slight dyspnea on exertion. Her exercise tolerance was otherwise good.

Physical examination revealed the following: blood pressure 106/70; heart not enlarged; typical presystolic rumble of mitral stenosis, with sinus rhythm; no signs of congestive failure.

CASE 3.—Mr. V. W., aged 25 years, was admitted to the hospital May 13, 1949, with chief complaint of coughing up blood. The patient gave a history of intermittent hemoptysis, usually after exertion, for two years. X-ray of the chest made two years previously had been noncontributory. Three days previous to admission the patient coughed severely, with moderate hemoptysis (sufficient to regurgitate into the nose). No other symptoms except slight dyspnea on exertion were present.

Physical examination revealed the following: blood pressure 130/70; mitral stenosis, with no cardiac enlargement; sinus rhythm; no signs of congestive failure. X-ray of the chest revealed clear lung fields; there was no evidence of mitral configuration. Electrocardiogram showed diphasic P waves and right axis deviation. The patient was discharged May 19, 1949, with his condition unchanged.

The patient was readmitted Oct. 2, 1949, with a history of persistent, severe hemoptysis of one week's duration. The physical findings were unchanged except for moderate anemia. The red blood cell count was 3 million, with 62% hemoglobin. Treatment consisted of small transfusions, the hemoptysis ceasing Oct. 6, 1949. A recent communication from his family physician stated that the patient had been seen recently, was feeling well, and was working.

The cases in this group are comparable with those designated by Bland and Sweet [6] as "tight mitral stenosis." This type of case associated with hemoptysis constitutes the greatest puzzle to the physician, since there usually is no genuine evidence of congestive failure and the exercise tolerance often is quite good. In only three of our cases did the history indicate that hemoptysis occurred after exertion. This fact is surprising, since apparently all observers agree that blood spitting occurs as a result of increased pulmonary hypertension. In the cases just summarized, the amount of blood varied from scanty to an amount sufficient (in one case) to produce moderate anemia. It seems reasonable to conclude, therefore (as did Wolff and Levine [3]), that hemoptysis in this group offers no prognostic significance. Not only were all these patients living after an average period of 36 months, but none of them had any significant cardiac enlargement. Of the five patients seen during the past year, the average length of time since onset of hemoptysis has been 45 months.

GROUP TWO

There was a striking difference in ratio of male to female in Group 2 as compared with Group 1, there being 12 males and one female. The onset of hemoptysis occurred at ages ranging from 18 to 41 years, with an average age of 33 years. Auricular fibrillation had developed in five cases, and there were aortic lesions in four. When these patients were last seen, the average length of time since onset of hemoptysis was 44 months.

Brief histories of a few cases in this group follow.

CASE 1.—Mrs. M. P., aged 42 years, had had rheumatic fever as a child. In 1944 there was beginning loss of cardiac reserve. In 1945, while in congestive failure, she coughed up bloody sputum. About two years previous to this report, while running a vacuum cleaner, she suddenly coughed up about a pint of bright red blood. There was no increased dyspnea before or after this episode, and she did not go to bed. She was not on a digitalis regimen at that time. There had been no hemoptysis since. During the two weeks previous to examination marked congestive failure had developed.

Physical examination revealed the following: blood pressure 92/60; bilateral hydrothorax; aortic and mitral stenosis and insufficiency; auricular fibrillation with extreme cardiac enlargement.

The patient responded well to treatment and was discharged in one week, much improved.

CASE 2.—Mr. R. F., aged 29 years, had had rheumatic fever at the age of 16. There was beginning loss of cardiac reserve five years previous to this report, with dyspnea on exertion. About four and one-half years previous to this report he had hemoptysis with a bout of left-sided failure. He was relieved by a "shot" after coughing up large quantities of bright red blood, and the coughing continued until hospital admission. On this occasion the hemoptysis was not associated with dyspnea nor with orthopnea.

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Physical examination revealed the following: blood pressure 100/70; heart enlarged to the left; typical murmurs of mitral stenosis and insufficiency; minimal passive congestion of lungs. X-ray of the chest showed enlargement of the left auricle, with mitral configuration and slight passive congestion.

The patient was treated expectantly with maintenance doses of digitoxin and sedation. Hemoptysis continued, subsiding in six days.

CASE 3.—Mr. J. L. L., aged 39 years, was seen in August, 1947, giving a history of rheumatic fever at the age of 3 years. There had been gradual loss of cardiac reserve since 1940. In April, 1946, he coughed up some blood. He was in frank failure in December, 1946. The patient when last seen was dyspneic on exertion; there was orthopnea but no edema.

Physical examination revealed the following: blood pressure 150/80; lungs clear; mitral stenosis with auricular fibrillation. Marked cardiac enlargement was revealed by examination and fluoroscopy.

We have been informed that this patient died in congestive failure in May, 1949.

CASE 4.—Mr. C. N. A., aged 37 years, had had rheumatic fever at the age of 20. Valvular involvement was noted 10 years previous to this report. He was dyspneic and had raised blood eight months previous to this report. Two weeks previous to being seen, he had another attack, with hemorrhage. There was no edema, and no dyspnea on exertion.

Physical examination revealed the following: blood pressure 130/84; lungs clear; moderate enlargement of heart; mitral stenosis, with sinus rhythm.

The patient was seen again Jan. 19, 1948, with a history of recent severe hemorrhage. He knew of no reason for the attack and has been well since, with no symptoms of congestive failure. His lungs were clear.

When seen again Nov. 9, 1948, the patient's condition was unchanged. (This patient is known to be still living.)

Evaluation of this group offers the most difficulty. Classification was attempted by determining from the history, to the best of our ability, whether or not the hemoptysis occurred while the patient was not in congestive failure, although four patients had a history of congestive failure prior to onset of hemoptysis. It is recognized also that some of these patients may have had normal-sized hearts at the time of hemoptysis, several years before a record was made of the heart size. Ten patients in this group are known to be alive, and all but two have been seen in the past year by one of us. Three, or 23 per cent, have died 17 months, 38 months, and 10 months, respectively, after onset of hemoptysis. In the series of cases reviewed by Wolff and Levine,[3] 22 of which would appear to fall in this group, 11 were dead at the end of six months after onset of hemoptysis. Of the 12 cases in our group with an adequate follow-up (the 13th case having been followed for only one week after onset), all survived for six months, 11 survived for one year, 10 for two years, and six are known to have survived for four years or longer. Although any accurate evaluation from a statistical standpoint could be made only if all the cases had been followed until death, it seems likely that these patients survived as long as they could have had they never had a hemoptysis.

GROUP THREE

Six cases fell in Group 3, four of these being males and two females. The patients' ages ranged from 16 to 45 years, averaging 33.5 years at the time of onset of hemoptysis. Half of the number had fibrillation and four had aortic lesions. Three (50%) of these patients are now dead.

Brief reports of representative cases in this group follow.

CASE 1.—Mr. E. J., aged 33 years, had had rheumatic fever at the ages of 12 and 16 years. He was unable to work for two years because of extreme lack of cardiac reserve. Marked orthopnea and edema developed one month previous to hospital admission.

Physical examination revealed the following: blood pressure 150/60/0; moderate respiratory distress; marked pulmonary congestion; extreme enlargement of the heart, with aortic and mitral stenosis and insufficiency; liver enlarged; grade-4 edema of the legs. Fluoroscopy of the chest revealed marked enlargement of all chambers of the heart and marked pulmonary congestion. The electrocardiogram was interpreted to show left bundle branch block.

This patient's course continued downhill. Twelve days after admission to the hospital he began spitting up moderate quantities of dark red blood, continuing to do so until he died, two days later.

CASE 2.—Mrs. B. B., aged 46 years, was admitted to the hospital Oct. 20, 1949, with a history of rheumatic fever in 1925. She complained of paroxysmal nocturnal dyspnea of two years' duration, with blood-streaked sputum one year previous to admission. She had had marked orthopnea for one week.

Physical examination revealed the following: blood pressure 128/74; moisture in the right lung base; aortic and mitral stenosis and insufficiency, with auricular fibrillation; heart moderately enlarged. (This patient is known to be still living.)

CASE 3.—Mrs. P. R., aged 32 years, was admitted to the hospital June 20, 1948, with no history of rheumatic fever or chorea. Onset of cardiac symptoms with failure occurred near term of a previous pregnancy four years ago. The patient was in the seventh month of pregnancy when seen for cardiac symptoms, onset of dyspnea and orthopnea having occurred two weeks previously. On the day before admission to the hospital, she coughed up a moderate amount of blood which was bright red. This was her seventh pregnancy, with no abortions.

Physical examination revealed the following: blood pressure 100/60; acute pulmonary edema present, also mitral stenosis, with auricular fibrillation; heart moderately enlarged. X-ray of chest revealed prominence of left ventricle, mitral configuration, and marked pulmonary congestion. The patient responded well to treatment, and subsequently was delivered at term with no difficulty.

In all the cases in this group the only stress necessary for hemoptysis to occur was the burden of congestive failure, with the added burden of pregnancy in the first trimester in one case (Mrs. P. R.). Whereas all patients in Group 1 and all but one patient in Group 2 had had repeated bouts of hemoptysis, only one in Group 3 had had more than one bout. None of these patients had massive hemoptysis; two instances were described as moderate. Three patients are dead; two days, five days, and 50 months, respectively, after onset of hemoptysis. The average period of survival for the entire group was 14 months, while that for the number known to be dead was 19 months. Although congestive failure is in itself an ominous prognostic sign, it would appear that hemoptysis in this group increases the likelihood of impending death.

SUMMARY

Of 168 cases of clinically diagnosed mitral stenosis seen both in the hospital and in private practice, 29 carried a history of hemoptysis. Cases were not included in this group unless the sputum was heavily streaked with blood or consisted almost entirely of frank blood. The amount of blood raised varied and, although as much as a pint was raised in some cases, it was never a serious

threat to life. The amount of blood coughed up had no prognostic significance since several of the patients who suffered the largest hemorrhages subsequently have done best.

Prior to the suggestion by Ferguson [5] and his associates that hemoptysis in mitral stenosis is due to rupture of varices of the bronchial veins, no plausible explanation of this symptom had been offered, and while the idea is credible, proof that such rupture actually is the mechanism producing the hemorrhage is not conclusive since several patients in this series underwent bronchoscopy with no bronchial varices being noted.

An attempt has been made to place these patients in three groups, largely on the basis of heart size and the presence or absence of congestive failure. Group 1 includes patients with slight or no cardiac enlargement and no congestive failure. Group 2 includes those with moderate to great cardiac enlargement and no congestive failure. Group 3 includes those with moderate to great cardiac enlargement, with congestive failure.

Patients in Group 1 correspond to those considered by Bland and Sweet [6] to have "tight mitral stenosis." These observers noted that acute pulmonary edema in their patients was at times associated with hemoptysis. In several of our cases the patients were suffering from acute pulmonary edema at the time of their hemoptysis, but in most instances this was not true. In three cases in this group, hemorrhage was severe but not dangerous. The threat of pulmonary edema is a more compelling reason for the venous shunt operation devised by Bland and Sweet than is the danger of subsequent hemorrhage. All our patients in this group have had more than one episode of bleeding, but their prognosis has nevertheless been good. All cases have been observed for an average follow-up period of 36 months, and none has shown any appreciable deterioration. The predominance of females in this group, as noted also by Bland and Sweet,[6] is striking.

Thirteen patients have been seen who had had one or more episodes of hemoptysis, and who had moderate or great cardiac enlargement, who were not in congestive failure at the time hemoptysis occurred. In some of these cases congestive failure subsequently has developed, but a particular effort was made to determine that congestive failure was not present at the time of hemorrhage before including the case in this group. In most instances, careful follow-up in these cases has shown that hemoptysis was an isolated episode and not related to any worsening of the patient's cardiac condition. In some of these cases the failure of hemoptysis to alter the patient's prognosis was very impressive. Six patients in this group have survived for more than four years, and several of them have continued at their usual occupation.

Six patients who had large hearts and who were in congestive failure have had hemoptysis. Two of these died of congestive failure in two days and five days, respectively, after hemorrhage. One patient lived for 50 months, and died in recurrent congestive failure. The three survivors do not provide a statistically significant follow-up. It appears that patients with mitral stenosis in congestive failure who have hemoptysis probably do not do so well as those not suffering a hemoptysis. In view of the beneficial effect of reducing blood volume by venesection in congestive failure, this situation is difficult to explain. It is possible that study of a larger number of cases in this group will reveal that hemoptysis has not actually contributed significantly to the decline of the cardiac condition.

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ETIOLOGY AND TREATMENT OF SERUM POTASSIUM DEFICITS

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Disturbances in the metabolism of potassium are a problem of clinical significance. The study of the behavior of this ion in disease was accelerated by the development of the flame photometer.[1] This instrument has allowed rapid quantitative determinations to be made in volume. Considerable information, primarily on a research basis, has accumulated concerning mechanisms of shifts in body potassium [2] and the symptoms and signs associated with these changes.[3] Relatively little information, however, has been tabulated concerning the prophylaxis or therapy of potassium deficits, except in a few selected situations, such as infantile diarrhea,[4] diabetic acidosis,[5] and a small series of postoperative patients.[6]

The following report summarizes briefly the mechanisms responsible for deficits of potassium and the associated clinical symptomatology. Actual experience as to the etiology and treatment of potassium deficits in 150 patients is tabulated and discussed, with recommendations concerning treatment schedules.

This work was aided in part by grants from the United States Public Health Service, and the Don Baxter Co., Glendale, Calif.

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MECHANISMS CAUSING DEFICITS OF POTASSIUM

Intracellular and Extracellular Potassium Deficits.—In general, there are two mechanisms which may cause loss of potassium from both the intracellular and extracellular compartments of the body. The first is inadequate intake of potassium. This occurs when food intake is restricted and parenteral fluids which do not contain

potassium are used. Potassium deficits arise in such situations because the urine is never potassium-free, and the ion continues to be lost from the body although none is supplied.[7]

The second mechanism is the accelerated loss of potassium from the body. The two major routes for the excretion of potassium, in health, are the urine (90%), and the stool (10%). Increased excretion in the urine may occur because of altered tubular function, with impaired reabsorption. Altered tubular function may be caused by changes in pH, notably alkalosis,[8] shock, anoxia, hormones (desoxycorticosterone acetate),[9] and pathological changes in the tubules secondary to various types of renal disease, such as the healing stages of the upper or lower nephron nephrosis,[10] rare forms of primary renal tubular disease, and occasional instances of chronic glomerulonephritis. Accelerated potassium excretion in the urine also occurs in any state associated with a negative nitrogen balance of any etiology as potassium, often in excess of the nitrogen loss, moves out of the cells with nitrogen during tissue catabolism.[2] This action has been demonstrated recently secondary to corticotrophin (ACTH) and cortisone therapy.[11] Administration of large volumes of isotonic saline may cause loss of potassium by diuresis.[12] Increased loss of potassium in the urine also occurs with dehydration.[2e]

Since 6 to 7 L. of gastrointestinal fluid—gastric juice, bile, pancreatic fluid, intestinal fluid—with a potassium concentration which varies but is usually approximately equal to or higher than that of the extracellular fluid [13] is secreted daily into the intestinal tract and reabsorbed, important loss of potassium from the body may occur if the gastrointestinal content is lost via fistulas of any type, nasogastric suction apparatus, or diarrhea.

Deficit of Extracellular Potassium.—Rapid shifts of potassium from the serum and interstitial fluid into the cells of the body occur because of the effect of drugs or other substances which accelerate either carbohydrate or protein synthesis. Thus, insulin,[14] large amounts of dextrose,[15] and testosterone [16] cause a shift of potassium from the extracellular to the intracellular compartment. The rare disease known as familial periodic paralysis [3] also causes a rapid shift of potassium from the extracellular to the intracellular fluid. Any factor, as administration of large volumes of parenteral fluid, that results in hemodilution will also cause a drop in serum potassium concentration.[12]

The serum potassium level is adequate for most clinical purposes, since the symptomatology of potassium deficits can usually be correlated with the serum concentration. Also, the intracellular levels (which cannot be determined) are usually reflected by the serum concentration if hydration and renal function are normal.

SYMPTOMS AND SIGNS OF POTASSIUM DEFICIT

Symptoms and signs of potassium deficit have usually been related to the change in the serum potassium level. (Some workers feel that the balance between the extracellular and intracellular components may be the more important factor.[17] Decreased serum potassium concentration affects neuromuscular physiology involving skeletal muscle, cardiac muscle, and the smooth muscle of the gastrointestinal tract. Weakness to paralysis of the muscles of the trunk and extremities (rarely the muscles supplied by the cranial nerves) may occur when the serum potassium level falls below 8 to 10 mg. per 100 cc. (2.05 to 2.56 mEq. per liter).[18] Changes in conduction, irritability, and contractility of cardiac muscle occur with levels under 10 to 12 mg. per 100 cc. (2.56 to 3.07 mEq. per liter). These changes are manifested by alterations in the electrocardiogram,[3] consisting of prolongation of the Q-T interval, and occasionally the P-R interval, S-T depression, and decrease in amplitude and change in contour of the T waves. Clinically, systolic murmurs and gallop rhythms, cardiac dilatation, and hypotension have been noted. If the potassium deficit is severe, cardiac arrest and death may occur. Actual necrosis of cardiac muscle has been produced by potassium depletion.[19] Lowered serum potassium may affect the musculature of the gastrointestinal tract to cause decreased motility and inhibition obstruction (adynamic ileus).[20]

INCIDENCE AND CAUSE OF POTASSIUM DEFICIT IN 150 PATIENTS

In the two-year period March 1, 1948, to March 1, 1950, there were 6,196 serum potassium determinations made in patients in a 3,000 bed hospital. The flame photometer mentioned earlier was used in these studies. Results in 1,803 (29.1%) determinations were lower than 15 mg. per 100 cc. (3.84 mEq. per liter) and 383 (6.2%) were higher than 23 mg. per 100 cc. (5.89 mEq. per liter), giving a total of 35.3% abnormal determinations. (The normal range for serum potassium in our laboratory is 16 to 22 mg. per 100 cc. [4.1 to 5.6 mEq. per liter].) The increasing number of determinations per month, as more knowledge of

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and interest in electrolyte problems developed, is clearly demonstrated by the increase from 26 serum potassium determinations in March, 1948, to 509 determinations in August, 1949.

The figure of 6,196 determinations represents approximately 3,098 patients. This figure is estimated on the basis that each patient had two potassium determinations. (This estimation was obtained from the figures for two periods—January, 1949, and November, 1949—when each patient had 1.7 and 2.08 determinations, respectively.) The number of patients with a low serum potassium level, using the figure of two determinations per patients, would be approximately 1,000 for the two-year period. (This is in a hospital of 3,000 beds.)

One hundred and fifty of these patients, the majority of whom were seen by us in the six-month period from January to July, 1949, form the basis of this report. (We constituted a committee who supervised potassium therapy during this six-month period, until the problems involved became adequately clarified and the procedures standardized.) There were 100 patients who had medical conditions or unoperated surgical conditions, and 50 postoperative surgical patients. The vast majority of the patients (122, or 81%) had gastrointestinal disorders, such as intestinal obstruction, cholecystic disease, peritonitis, pyloric obstruction, pancreatitis, and gastrointestinal malignancy. A small group (28, or 19%) were due to a variety of causes, as diabetic coma undergoing vigorous insulin therapy (10 patients), renal disease (five patients), and acute infection (five patients).

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Table 1 tabulates the basic etiology responsible for the low serum potassium in each patient. The significant role of poor or no potassium intake as a cause of low serum potassium is demonstrated since 131 of the 150 patients (87.4%) had decreased potassium intake. Ninety of these 131 patients were on nasogastric suction and were receiving parenteral fluids which did not contain potassium. The average period the patients were on nasogastric suction prior to the development of the low serum potassium was 5.3 days, plus an average of 7.5 days of poor or no food intake prior to the use of nasogastric suction. Forty-one of the patients were not on nasogastric suction but had had prolonged periods of poor or no food intake, averaging 16.3 days.

Nine (6%) of the 150 patients had a low serum potassium due to accelerated loss of potassium from the body via the urine or gastrointestinal tract—nasogastric suction, fistulas, or diarrhea.

Ten (6.7%) of the 150 patients had low serum potassium levels owing to the rapid shift of potassium from the extracellular fluid into the cells under the influence of insulin used in the therapy of diabetic coma.

TABLE 1.—*Basic Etiology of Potassium Deficiency in 150 Cases**

Basic Etiology of Deficiency	No. of Cases	Average No. of Days Basic Etiology Operative
I. Decreased Intake of Potassium		
A. Poor food intake or none	41	16.3
B. Nasogastric suction and potassium free parenteral fluids, plus previous poor food intake	90	5.3 of suction + 7.5 previous poor food intake
II. Increased Losses of Potassium from Gastrointestinal Tract or Urine		
A. Diarrhea	4	11
B. Ileostomy	1	14
C. Desoxycorticosterone (doca ®) therapy	2	5
D. Lower nephron nephrosis, recovery phase	2	3+
III. Shift of Potassium into the Cells: Diabetic coma under therapy with insulin	10	1
Total	150	

* Acid-base balance analyzed separately. See text.

The importance of alkalosis as a cause of serum potassium deficits is demonstrated by the fact that 64 (42.7%) of the patients had alkalosis, in addition to the mechanisms listed in Table 1. Acidosis was present in 15 patients (10%), occurring primarily in those patients with diabetic coma or diarrhea. Thirty-six per cent of the patients had a normal carbon dioxide combining power, and 11.3% had not had a determination of the carbon dioxide combining power.

While it was frequently impossible to evaluate the symptoms and signs due to hypopotassemia in the presence of a serious primary disease, an attempt was made to determine the relation of the serum potassium level to the state of the patient and the outcome. The clinical condition of 34 patients (22.6%) with a serum potassium under 10 mg. per 100 cc. (2.56 mEq. per liter) was very poor, as evidenced by such findings as profound muscle weakness, inhibition obstruction (adynamic ileus), cardiac dilatation, hypotension, and gallop rhythms.

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Electrocardiograms were taken on many of the patients. These tracings showed the characteristic changes described in hypopotassemia in the majority of instances.

In retrospect, 10 patients (6.7%) may well have died of hypopotassemia.

TREATMENT RESULTS

The problems in therapy resolved themselves into three considerations: (1) the best type of solution to use and the mode of administration, (2) the prophylactic requirement for potassium in patients who were not eating, and (3) the average amount of potassium required to correct acute and chronic deficits.

Type of Solution.—The solution to be used for the prophylaxis and treatment of potassium deficits in a large hospital had to be simple to prepare and in such form as to be practical for use in many different types of electrolyte imbalance. For these reasons we used potassium chloride, 1 gm. in 15 cc. of distilled water, prepared in vials and autoclaved, as our stock solution for intravenous use. The proper number of grams of potassium could then be added to whatever intravenous solution was required for other purposes, as dextrose in water.

TABLE 2.—*Potassium Requirement Calculated from Balance Studies*

Diagnosis	Potassium in Urine (Range) Gm.	Potassium in Naso-gastric Suction Fluid (Range) Gm.	Total Potassium Lost (Range) Gm./24 Hr.	Total KCl Required on Basis of Measured Loss, Gm./24 Hr.
Appendectomy for perforated appendix	1.1 to 1.7	0.06 to 0.3	1.2 to 1.76	2.4 to 3.5
Repair of duodenal perforation (stab wound)	0.6 to 1.8	0.1 to 0.4	0.9 to 1.8	1.8 to 3.6
Gastro-enterostomy and vagotomy for pyloric obstruction (peptic ulcer)	1.4 to 2.0	0.02 to 1.1	1.4 to 3.1	2.8 to 6.1
Ileostomies for recurrent volvulus	0.96	0.54	1.5*	2.0

* Received 0.5 gm. K.

isotonic saline, ⅙ molar sodium lactate, or 0.9% ammonium chloride.

For prophylaxis of potassium deficits we used a 0.1 to 0.2% solution of potassium chloride (1 to 2 gm. of potassium chloride per liter of any type of intravenous fluid required) given no faster than 1 L. (1 gm.) per hour. For therapy of serious potassium deficits we used a 0.3 to 1.0% solution (3 to 10 gm. of potassium chloride per liter of any type of intravenous fluid required), administered slowly and followed by frequent serum potassium determinations or electrocardiograms. (This solution is hypertonic and may cause pain in the vein. We have seen no thrombi from its use.) Potassium has also been administered in any of the fluids which can be given by hypodermoclysis, in 0.1 to 0.2% concentration, without local reactions.

For oral administration we used a 1% potassium chloride solution, as it was frequently necessary to administer this medication through a nasogastric tube.

Prophylaxis of Deficits.—Table 2 shows the average daily loss of potassium via the urine and in the nasogastric suction fluid in four patients who were not receiving potassium and in whom potassium balance studies were done. The daily potassium requirement in these patients, expressed as grams of potassium chloride, varied from 1.8 gm. to 6.1 gm.

The 24-hour loss of potassium in nasogastric suction fluid varied in our patients from 0.1 to 1.4 gm. The concentration of potassium in the gastric fluid varied from 5 to 51 mg. per 100 cc. (1.3 to 13.1 mEq. per liter) with an average of 20 to 30 mg. per 100 cc. (5.12 to 7.68 mEq. per liter). An average range of urinary potassium loss cannot be given, since the amount varied widely, depending on the serum potassium concentration, the urine volume, renal function, and pH of the blood.

The prophylactic requirement of potassium chloride to maintain a normal serum potassium level in five patients receiving parenteral fluids for several days varied from 2 to 6.4 gm. of potassium chloride, with an average of 4 gm. While such studies are obviously less accurate than balance studies, since the amount of potassium required is not known unless the urinary potassium excretion is measured, certain information can be obtained from them concerning range of dosage.

From such studies we concluded that 3 to 6 gm. of potassium chloride daily is an average prophylactic amount for patients requiring several days of parenteral fluid therapy. We prefer to err on the side of too much rather than too little potassium for prophylaxis, since excess potassium is readily excreted by the kidney unless renal function is seriously impaired.

Treatment of Acute and Chronic Deficits.—Our experience in the correction of potassium deficits has developed with practice and is documented, with illustrative examples from the series of 150 patients, in Tables 3, 4, and 5.

With a large staff of interns and residents, considerable caution was entertained early with regard to rapid correction of deficits, because of the potential dangers of intravenous potassium therapy. If symptoms were not alarming, it was felt wiser to take several days to correct deficits. Thus, early, far too little potassium was given per day (2 to 6 gm. of potassium chloride), so that many days elapsed before the serum level became normal. With low serum potassium levels of long standing, large amounts of potassium are required, as can be seen in Table 3, where in 15 patients the requirements for correction of the serum level varied from 8 to 35 gm. of potassium chloride given over a period of 3 to 21 days.

Table 4 illustrates more rapid, competent correction of acute and chronic potassium deficits. This Table also illustrates the difference in the amount of potassium chloride required to correct acute deficits (3 to 9 gm.), as contrasted with chronic deficits associated with serious cellular depletion (33 to 40 gm.).

As the result of our studies, shown in Tables 3 and 4, we now give 3 gm. of potassium chloride intravenously in 24 hours for the correction of acute deficits. This is in addition to the prophylactic maintenance dose of 3 to 6 gm. For serious, chronic deficits we now give 10 to 20 gm. of potassium chloride intravenously in 24 hours, or 10 gm. intravenously and 10 gm. orally, if the oral route can be used.

As soon as patients are able to eat, potassium deficits usually cease to be a problem since an adequate amount of potassium can be obtained from the average diet for maintenance and gradual correction of deficits. For this reason we have laid little stress on oral potassium; usually, if the patient is able to take oral medications,

some form of diet can also be taken. Oral potassium in liquid form has been administered to some patients through a nasogastric tube. It has also been used to supplement the dietary intake of potassium in some instances.

The results of potassium therapy in five patients with diabetic coma are listed separately, as this is a somewhat special problem. In patients 1, 2, and 3 in Table 5, potassium administration was started early in the course chloride to all patients in diabetic coma during the first 24 hours of intensive insulin therapy, starting as soon as serious dehydration is corrected and renal function is known to be adequate. Two to 4 gm. of potassium chloride is given intravenously as a 0.1 to 0.2% solution, and 10 to 12 gm. orally as a 1% solution.

There were several infants and children in our series of 150 patients with potassium deficits. The majority of these patients had infantile diarrhea. In most instances

TABLE 3.—*Results of Potassium Therapy*

Diagnosis	Serum Potassium Before Treatment: Mg. per 100 Cc.	Serum Potassium Before Treatment: mEq. per L.	Serum Potassium After Treatment: Mg. per 100 Cc.	Serum Potassium After Treatment: mEq. per L.	Duration of Treatment, Days	Amount Potassium Chloride Used for Treatment: I.V., Gm.	Amount Potassium Chloride Used for Treatment: Oral, Gm.	Amount Potassium Chloride Used for Treatment: Total, Gm.
Relief of small bowel obstruction *	9	2.3	17	4.35	4	7	22	29
Pyloric obstruction, ulcer *	10	2.56	16	4.1	18	38	..	38
Pyloric obstruction, ulcer *	11	2.82	16	4.1	7	21	..	21
Vomiting, etiology undetermined †	11	2.82	19	4.86	5	21	..	21
Hysterectomy (fibromyomata) ‡	13	3.33	20	5.12	7	24	..	24
Abdominal exploration (carcinoma of pancreas) ‡	12	3.07	20	5.12	4	10	45	55
Gastric resection (carcinoma of stomach) †	9	2.3	18	4.61	5	24	..	24
Colon resection (carcinoma of colon) ‡	8	2.05	14	3.58	5	27	26	53
Appendectomy, perforated appendix *	11	2.82	17	4.35	7	12	11	23
Gastroenterostomy (gastric carcinoma) †	11	2.82	18	4.61	21	42	..	42
Cholecystostomy (cholecystitis and cholangitis) *	12	3.07	24	6.14	6	33	..	33
Abdominal exploration, hepatitis †	10	2.57	19	4.86	12	18	40	58
Pyloric obstruction, ulcer *	12	3.07	17	4.35	3	11	..	11
Pancreatitis ‡	12	3.07	18	4.61	9	13	10	23
Excision of bleeding peptic ulcer †	9	2.3	15	3.84	3	8	..	8

* Small amount liquid diet.
† No food intake.
‡ Soft diet.

TABLE 4.—*Potassium Requirements in Chronic Versus Acute Potassium Deficits*

Diagnosis	Serum Potassium: Mm. per 100 Cc.	Serum Potassium: mEq. per L.	Time to Correct Deficit, Days	Intake/Potassium: Intravenous, Gm.	Intake/Potassium: Oral, Gm.	Intake/Potassium: Total, Gm.	Output/Potassium: Urine, Gm.	Output/Potassium: Gastric, Gm.	Output/Potassium: Total, Gm.	Balance Potassium for Period, Gm.	Total KCl Required to Correct Deficit, Gm.
Chronic											
Poor food intake plus diarrhea	7-20	1.79-5.12	3	3	15	18	0.52	...	0.52	17.48	33 *
Colostomy, colectomy and nephrectomy for carcinoma of colon	8-27	2.1 -6.86	2	10	10.5	20.5	0.65	...	0.65	19.85	39.70
Acute											
Pyloric obstruction (peptic ulcer) with acute alkalosis	11-17	2.82-4.35	2	6.9	....	6.9	5.0	0.3	5.3	1.6	3.2
Appendectomy for perforated appendix, generalized peritonitis	11-17	2.82-4.35	7	10.58	1.62	12.2	6.4	1.1	7.5	4.7	9.4

* Plus potassium in diet.

TABLE 5.—*Therapy of Potassium Deficits in Diabetic Coma (During 24-Hr. period)*

Patient	Serum Potassium: Start of Therapy, Mg. per 100 Cc.	Serum Potassium: End of Therapy, Mg. per 100 Cc.	Serum Potassium: Start of Therapy, mEq. per L.	Serum Potassium: End of Therapy, mEq. per L.	Potassium Intake: Intravenous, Gm.	Potassium Intake: Oral, Gm.	Potassium Intake: Total, Gm.	Potassium Output Urine, Gm.	Potassium Balance, Gm.	Total Potassium Chloride Required, Gm.
1	19.5	18.7	4.99	4.75	...	6.76	6.76	1.57	5.19	10.38
2	16.5	16.5	4.2	4.2	...	9.14	9.14	4.7	4.44	8.88
3	22.2	24.5	5.6	6.27	...	6.80	6.80	0.97	5.83	11.66
4	11	17	2.82	4.35	3.5	7.8	11.3	1.06	10.24	20.48
5	9.2	22	2.36	5.6	...	8.22	8.22	2.14	6.08	12.16

of the treatment of the diabetic coma, with the result that the serum potassium was maintained at a normal level throughout treatment. In patients 4 and 5, therapy was started only after a drop in the serum potassium had occurred. The amount of potassium required to correct the body potassium deficit in these five patients ranged from 8.88 to 20.48 gm. of potassium chloride in 24 hours.

As the result of the above experience and other studies in diabetic coma,[5c] we now give 12 to 16 gm. of potassium we used the formula recommended by Govan and Darrow [4] for infants and children (0.20 gm. of potassium chloride per kilogram of body weight per 24 hours).

HIGH SERUM POTASSIUM LEVELS

For completeness, it might be briefly stated that high serum potassium concentrations occur because of impaired glomerular filtration, hemoconcentration, rapid tissue breakdown, or too rapid intravenous administration of potassium. Therapy is frequently difficult. The

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type used depends on the etiology of the increased level, and includes extrarenal removal of potassium by such procedures as the artificial kidney, renal removal by diuresis induced by large volumes of isotonic saline administered intravenously, shift from serum into the cells by use of insulin and dextrose, and antagonism of the physiological effects of high serum potassium by the use of calcium. In our series, high serum potassium levels were usually associated with impaired renal function or hemoconcentration.

COMMENT

Our clinical results are in accord with present concepts of the mechanisms of potassium loss as outlined above. The largest number of deficits occurred in patients with poor or no intake of potassium, and many were related to the occurrence of alkalosis. A smaller number of serum potassium deficits were due to accelerated loss from the body via gastrointestinal content loss, urinary loss, or rapid shift into the cells in the therapy of diabetic coma.

While the gross mechanisms of potassium changes in the body are known, many of the fundamental problems, such as the mechanisms by which potassium enters the cell against a high diffusion gradient, the factors governing tubular reabsorption, and the forces that prevent cellular potassium from being supplied to correct serious but small extracellular deficits, are unsolved.

Since the normal kidney can conserve potassium rigorously in the face of need, it is hard to understand why, in the presence of a supply of potassium from tissue breakdown (this occurs in most postoperative patients or patients who are not eating), the serum level cannot be maintained. In some patients, factors, such as alkalosis or shock, which alter the ability of the kidney to conserve potassium are known, but in other patients the mechanisms are obscure and may well be hormonal. In this regard we have seen a few patients on nasogastric suction receiving potassium-free parenteral fluids, who nevertheless maintained a normal serum potassium level for some time (five to 10 days). This is presumably owing to the derivation of potassium from tissue breakdown, combined with decreased renal excretion.

The two major problems in therapy are the hazard of intravenous potassium administration and the estimation of the amount of potassium required to correct deficits. The hazard of intravenous therapy lies in the narrow range of normal serum potassium 16 to 22 mg. per 100 cc. (4.1 to 5.6 mEq. per liter) and the small amount of potassium in the total extracellular fluid (1.5 to 2.5 gm.). Small alterations in the serum potassium may be lethal, since death due to cardiac standstill occurs at serum potassium levels between 40 and 50 mg. per 100 cc. (10.26 to 12.8 mEq. per liter). One to 2 gm. of potassium given rapidly may cause such a concentration. This is avoided by dilution of the potassium in a liter of fluid.

When a serious potassium deficit associated with symptoms is present, large amounts of intravenous potassium are urgently required. If frequent serum determinations cannot be made, the direct writer electrocardiogram is an excellent method of following the serum potassium level.[21] With the use of serial tracings, a fairly good estimation of the serum concentration can be made from the character and height of the T waves. Potassium can be given safely until the T waves become high and peaked.

Since the body store of potassium is approximately 150 to 175 gm., most of which is in the cells, 20 to 40 gm. of potassium chloride may be required to correct serious deficits. In such circumstances, intravenous therapy appears to be of little hazard since there is a rapid shift of the administered potassium into the depleted cells.

While we were well aware of the value of previously recommended repair and prophylactic fluids [22] (particularly those containing such ions as calcium, magnesium, and phosphate), we were faced with the problem of being unable to obtain more than one solution for both prophylaxis and repair of potassium deficits. Also, we prefer to "tailor make" repair solutions to meet the particular electrolyte problem involved. This is done most easily by the use of stock solutions of potassium, calcium, or magnesium, added to the ordinary standard intravenous fluids, such as isotonic saline and 5 to 10% dextrose in water or saline, in the amounts required to correct the particular deficit or deficits.

SUMMARY

In the two-year period, March, 1948, to March, 1950, 6,196 serum potassium levels were determined. Of the levels, 29.1% were low and 6.2% were high. Approximately two serum potassium determinations were done per patient.

The disease entities and the mechanisms responsible for serum potassium deficits in 150 patients, the majority of whom were seen during a six-month period by us, are tabulated. One hundred and thirty-one (87.4%) patients had various types of gastrointestinal disorder. Ninety patients (60%) were on nasogastric suction and were receiving no potassium in their parenteral fluids. They had an average of 7.5 days of poor or no intake of food before suction was started and an average of 5.3 days on suction before the serum potassium was found to be low. Forty-one patients (27.4%) who were not on nasogastric suction had had a prolonged period of poor or no food intake, averaging 16.3 days. As to the role of acid-base balance, 42.7% of the patients had alkalosis, 10% acidosis, 36% a normal carbon dioxide combining power, and 11.3% had no determination of the carbon dioxide combining power.

Results of therapy are listed. As the result of our studies, the following treatment schedule is suggested for adults. For prophylaxis of potassium deficits, in patients who are not eating and are maintained on parenteral fluids, 3 to 6 gm. of potassium chloride intravenously is required daily in 0.1 to 0.2% concentration (1 to 2 gm. per liter of whatever intravenous solution is required).

For the correction of deficits assuming adequate renal function the following is suggested:

For recent, acute deficits, 3 gm. of potassium chloride daily given intravenously as 0.1 to 0.2% solution until

21. Stephens, F. I.: Paralysis Due to Reduced Serum Potassium Concentration During Treatment of Diabetic Acidosis, Ann. Int. Med. **30**: 1272 (June) 1949.

22. Footnotes 4 and 5a. Burnett, C. H., and Barrows, B. A.: Repair Solutions in the Treatment of Metabolic Acidosis and Alkalosis, M. Clin. North America **32**: 1293 (Sept.) 1948.

deficit is corrected is recommended, in addition to the daily prophylactic dose.

In cases of diabetic coma undergoing treatment, 12 to 16 gm. of potassium chloride should be given during the first 24 hr. of intensive insulin treatment—2 to 4 gm. of potassium chloride intravenously (0.1 to 0.2% concentration), and 10 to 12 gm. orally. Therapy should be started as soon as dehydration is partially corrected and renal function is found to be adequate.

In severe chronic deficits, 10 to 20 gm. of potassium chloride should be given intravenously as a 0.3 to 1% solution, or 10 gm. intravenously and 10 gm. orally, if the oral route of administration is possible.

For infants the dosage schedule recommended by Darrow (0.20 gm. of potassium chloride per kilogram of body weight per 24 hours) may be used.

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HYPOVENTILATION SYNDROME IN BULBAR POLIOMYELITIS

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Because of the complex nature of respiratory inadequacy due to bulbar poliomyelitis and the severity of associated disturbances in acutely ill patients with this disease, there is little precise knowledge of the disturbed respiratory mechanism itself. In a patient whose muscles of respiration do not coordinate and whose respiratory air flow pattern is grossly irregular, it is sometimes difficult to tell whether the irregularity is caused by involvement of the respiratory center or by the airway difficulties engendered by cranial nerve involvement. Detailed attention to the maintenance of a clear airway, auscultation over the larynx, and visual observation of the character of the patient's respiratory effort often help to differentiate respiratory center involvement from the irregularity that arises as a result of the protective reflexes that are invoked to prevent the pulmonary aspiration of mucus and saliva.

The gross irregularity of breathing and the ventilatory inadequacy which may be associated are part of the classical picture of bulbar poliomyelitis, and have been adequately described by numerous observers. When a clear airway has been ensured and the respiratory defect persists, the latter is then attributable to respiratory center involvement. The nature of the defect may be apparent clinically in two ways: (1) gross irregularity of the rate and rhythm of respiration, and (2) incoordination of the various muscles of respiration. In addition, a third and perhaps more important type of respiratory defect occurs. This has received passing notice by the clinician,[1] but has not been subjected to precise investigation.

Aided by a grant from the National Foundation for Infantile Paralysis.

From the Department of Physiology, Harvard School of Public Health, and the Children's Medical Center, Boston.

1. Wilson, J. L.: Outline of Essential Treatment of Bulbar Poliomyelitis, in Poliomyelitis: Papers and Discussions Presented at the First International Poliomyelitis Conference, International Poliomyelitis Congress, Philadelphia, J. B. Lippincott Company, 1949, p. 245.

2. Dr. Charles A. Janeway and Dr. William Berenberg of the Children's Medical Center and Dr. Louis Weinstein of the Haynes Memorial Hospital in Boston allowed us to observe these patients and encouraged the study.

3. Sarnoff, S. J.; Maloney, J. V., Jr.; Sarnoff, L. C.; Ferris, B. G., Jr., and Whittenberger, J. L.: Electrophrenic Respiration in Acute Bulbar Poliomyelitis. Its Use in Management of Respiratory Irregularities, J. A. M. A. **143**: 1383 (Aug. 19) 1950.

4. Riley, R. L.; Proemmel, D. D., and Franke, R. E.: Direct Method for Determination of Oxygen and Carbon Dioxide Tensions in Blood, J. Biol. Chem. **161**: 621, 1945.

This third type of respiratory defect in bulbar poliomyelitis, or what shall be termed the hypoventilation syndrome, consists of a decreased sensitivity of the respiratory center to the partial pressure of carbon dioxide in arterial blood. This results in lowered pulmonary ventilation which, in these circumstances, is not attributable either to a compromised airway, to a significant defect of lower motor neurones or muscles of respiration, or to the incoordination of respiratory motor activity. It is attributable to a diminished respiratory drive, and in some ways is analogous to the situation in which the respiratory center has been depressed by an overdose of barbiturate. The hypoventilation syndrome is the subject of this communication.

During the course of an investigation of the management of respiratory difficulties in bulbar poliomyelitis, four patients were seen whose respiration was such as to include them for consideration in this category.[2] The first of these was a 17-year-old male with bulbospinal poliomyelitis, who at times breathed at a rate of only 4 respirations per minute and became cyanotic when permitted to lapse into these periods of bradypnea. Underventilation could be prevented, even though his mental state was somewhat clouded, simply by giving him fairly frequent and firm verbal orders to breathe. Later grossly irregular and inadequate breathing developed in this patient and he was treated with electrophrenic respiration during that period.[3] The second patient was a 43-year-old woman with bulbospinal poliomyelitis who exhibited the same phenomenon but was more refractory to voluntarily sustaining adequate ventilation because of her mental state. That is to say, she responded to single and repeated orders to breathe more deeply, but would not continue to do so for more than two or three breaths after the last command. The third and fourth patients were 9 and 11-year-old boys with bulbar poliomyelitis. Inasmuch as they were the only ones in whom quantitative data were obtained, only their cases will be reported in detail.

METHOD

Arterial blood gas tension analysis by the method of Riley and others[4] was begun within 20 min. after obtaining the samples. The arterial oxygen and carbon dioxide contents were determined by the method of

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Van Slyke and Neill.[5] Electrophrenic respiration (EPR) was administered by applying an intermittent electrical potential over the motor point of the phrenic nerve.[6] Respiratory air flow patterns were taken with the clinical pneumotachograph of Silverman and Whittenberger.[7]

REPORT OF CASES

CASE 1.—A. B., a boy aged 9 years who was admitted to the hospital Sept. 25, 1949, had had coryza and moderate headache for three days prior to admission. The following day a slight fever and stiff neck developed, and this was followed with difficulty in swallowing, a nasal voice, and regurgitation through his nose on the day before admission. On admission, the temperature was 102.4 F., pulse 104, and respirations 32. The patient was drowsy and irritable, and an accumulation of secretions was noted in the pharynx. He exhibited moderate stiffness of the neck, and spasm of the back and hamstring muscles. Both divisions of the left facial nerve were paralyzed. The tongue deviated slightly to the left and the palate to the right, with poor motion on both sides. There was thought to be slight weakness of the right anterior tibial muscle, and the left upper abdominal reflex was absent.

The cerebrospinal fluid contained 210 white blood cells, of which 80% were lymphocytes. The Pandy test for globulin showed a trace, the test for sugar being negative. The blood pressure remained in the vicinity of 110/80.

The patient's temperature fell to normal, and there did not seem to be any progression of the paralysis. Although the mental state was somewhat clouded, it was felt that the patient was doing reasonably well until 5:00 a. m. of Sept. 27, at which time it was noted that his respirations became quite shallow, without becoming either rapid or irregular, for varying periods of time, and that this hypoventilation was severe enough to cause a definite change in his color. Accordingly, oxygen was administered by nasal catheter. These periods of hypoventilation alternated irregularly with periods of apparently adequate ventilation until seen by us later that morning.

Observation of the patient during the subsequent six hours confirmed the above description of the patient's respiratory status. The alternation of periods of hypoventilation with periods of adequate ventilation occupied more prolonged time intervals than were consistent with Cheyne-Stokes breathing. There was no apparent regular periodicity or rhythm to the changes. Rather, the period of hypoventilation seemed to last as long as the patient was quiescent and undisturbed.

As soon as the patient was aroused, or spontaneously became restless, respiration returned to apparently normal proportions. To demonstrate further that the patient had full control of his respiratory muscles, it was but necessary to ask him to breathe forcefully. If urged, the patient was capable of performing inspiratory motions that appeared to approach the inspiratory limit of his vital capacity, with vigorous excursion of both his diaphragm and intercostal muscles.

Quantitative evidence was obtained concerning the blood gas tensions during these different phases of respiratory activity. The nasal oxygen was discontinued at 2:05 p. m. on Sept. 27; a needle was subsequently introduced into the right femoral artery, and three 10-cc. samples were obtained. The first was drawn at 2:55 p. m., after about two minutes of commanded hyperventilation. The needle was left in situ and the patient permitted to remain undisturbed with moderate hypoventilation until 3:12 p. m., at which time the second sample was drawn. The insertion of the syringe into the three-way stopcock at this time disturbed the patient a little and increased ventilation slightly, but nevertheless this sample showed evidence of significant hypoventilation. Electrophrenic respiration was then applied on the right side for seven minutes, with suppression of spontaneous respiration. At the end of this time the third sample was drawn. Table 1 lists the results. It is evident that during command ventilation the boy had sufficient voluntary control of his respiratory muscles to accomplish considerable hyperventilation as evidenced by the low pCO_2 and high pO_2. Likewise, stimulation of only one phrenic nerve, presumably active during spontaneous ventilation, was capable of maintaining a normal pO_2 and decreasing the pCO_2. In contrast to this are the low pO_2 and high pCO_2 which were present when the patient was left undisturbed to breathe according to the dictates of his diseased respiratory center.

CASE 2.—T. R. Q., a boy aged 11 years, was admitted to the hospital on Aug. 24, 1950, with a diagnosis of bulbar poliomyelitis. He had been well until the day preceding admission, when he had malaise, vomited three times, and had a rectal temperature of 103 F.

TABLE 1.—*Data on Patient A. B.; pO_2 and pCO_2 in Arterial Blood of Patient with Respiratory Center Involvement Due to Bulbar Poliomyelitis*

Type of Breathing	pO_2, Mm. Hg	pCO_2, Mm. Hg	Serum CO_2, Vol. %	pH	O_2 Content, Vol. %	O_2 Capacity, Vol. %	Saturation, %
1. Forced	115	34	62.03	7.53	.....	.....	....
2. Spontaneous	87	50	65.68	7.37	19.03	20.35	92.5
3. Electrophrenic respiration	98	27	65.98	7.65	.....	.....	....

Normal values: pO_2 95-100 mm. Hg; pCO_2 40 ± 2 mm. Hg; pH serum 7.40 ± .05 serum CO_2 55-60 vol. per cent (assuming the supine position and barometric pressure of 760 mm. Hg).

On admission his rectal temperature was 103.6 F., his pulse was 76, and his respirations were full and regular at 20 per minute. The patient was apprehensive, exhibited a nasal, gurgling speech, and was unable to swallow sips of water. Additional positive neurological findings were deviation of the tongue to the right, generalized left facial weakness, and slight stiffness of the neck and back. Saliva was puddled in the posterior pharynx.

On Aug. 24, a lumbar puncture showed 113 white blood cells, of which 83 were polymorphonuclear. On Sept. 2, nineteen white blood cells were present, all of which were mononuclear.

A pneumotachogram at 10:00 a. m. on Aug. 25, revealed an air flow pattern that deviated little or not at all from the normal and confirmed the impression gained from gross observation of the patient's breathing (Fig. 1). At 3:00 p. m. the air flow pattern became somewhat irregular and shallow and had pauses not usually seen in normal breathing. By 7:30 p. m. the patient's respirations exhibited the irregularity and the series of three or four rapid short breaths that resemble panting which are frequently seen in bulbar poliomyelitis. Arterial blood analysis on the morning of Aug. 25 revealed a pO_2 of 95 mm. Hg and a pCO_2 of 37 mm. Hg.

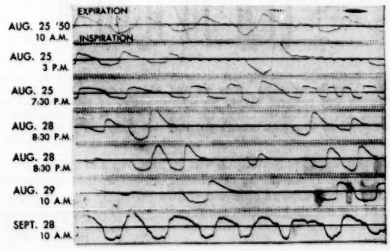

Fig. 1 (Case 2).—Pneumotachograms on patient T. R. Q. from Aug. 25 to Sept. 28, 1950. The progress from normal on Aug. 25, to abnormal and back to normal again on Sept. 28 can be seen.

5. Van Slyke, D. D., and Neill, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**: 523, 1924.

6. Sarnoff et al.[3] Sarnoff, S. J.; Sarnoff, L. C., and Whittenberger, J. L.: Electrophrenic Respiration (EPR). VII. The Motor Point of the Phrenic Nerve in Relation to External Stimulation, Surg., Gynec. & Obst., to be published.

7. Silverman, L.: Respiratory Air Flow Characteristics and Their Relation to Certain Lung Conditions Occurring in Industry, J. Indust. Hyg. & Toxicol. **28**: 183, 1946. Silverman, L., and Whittenberger, J. L.: Clinical Pneumotachograph, in Methods in Medical Research, Chicago, The Year Book Publishers, Inc., 1950, vol. 2, p. 104; Instantaneous Air Flow Measurements, ibid., pp. 215-218.

On the evening of Aug. 26, because the irregularities persisted, electrophrenic respiration was tested on this patient in anticipation of more serious difficulty. It was found to function well both on the left and right phrenic nerves. On this and subsequent occasions the application of electrophrenic respiration promptly suppressed all spontaneous respiration and was accompanied with a diminution or cessation of the patient's restlessness.

Although the irregular respirations persisted and the patient was frequently restless and disoriented, he was not thought to be hypoventilating except for brief periods. At these times verbal stimulation could re-establish apparently adequate ventilation, until 10:00 p. m. on Aug. 27, at which time his respiration became shallow and fell to between 6 to 8 per minute. Electrophrenic respiration was applied by external stimulation and maintained by means of the bedside clamp until 2:30 p. m. on Aug. 28, at which time, although still breathing irregularly, he was responsive and again able to maintain apparently more adequate ventilation than previously.

The arterial blood gas tensions obtained on the afternoon of Aug. 28 are shown in Table 2, and indicate the subnormal ventilation of this patient during spontaneous breathing. Soon afterward respiratory minute volumes were obtained several times while the patient was breathing room air and again while breathing 100% oxygen (Fig. 2). At 8:30 p. m. the pneumotachograms were still such as to indicate derangement of the respiratory center (Fig. 2).

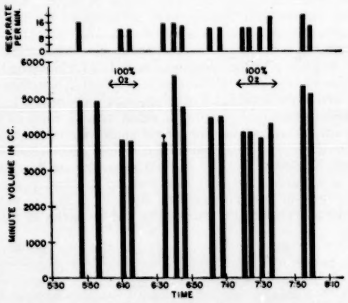

Fig. 2 (Case 2).—Respiratory rates and minute volumes of patient T. R. Q. while breathing room air and 100% oxygen. The decreased ventilation that occurred during the administration of 100% oxygen can be seen. The question mark over the value at 6: 34 p. m. indicates what was thought to be a leak occurring during that collection period.

On Aug. 29, the arterial pO_2 was 96 mm. Hg and the pCO_2 was 37 mm. Hg. It should be mentioned, however, that through an oversight the blood sample was drawn promptly after the insertion of the needle into the femoral artery, before the patient had a chance to quiet down from the reaction engendered by the needle puncture.

Again at 1:00 a. m. on Aug. 30, respirations became shallow and fell to between 0 and 4 per minute, and the patient did not react to either verbal or physical stimuli. Electrophrenic respiration was again promptly applied and maintained until 8:00 a. m., at which time he was again able to maintain apparently adequate ventilation. Since it was felt that a catastrophe had been only narrowly avoided, the implantation of a phrenic electrode was considered so as to maintain adequate ventilation until the patient was clearly over his respiratory defect. The use of the tank respirator was not felt to be indicated in this case. At this point, however, the patient began to improve noticeably, and further respiratory support was not required. The patient was discharged on Sept. 12, and a follow-up pneumotachogram on Sept. 28, 1950, showed a normal respiratory air flow pattern.

COMMENT

It becomes likely, in view of the data obtained on these patients, that a third type should be more clearly recognized in the classification of central respiratory defects in bulbar poliomyelitis. That is, in addition to irregularities of rhythm and incoordination of muscular effort, one must postulate that an altered sensitivity to CO_2 may occur presumably as a result of involvement of the respiratory center. Sedation had not been administered to these patients. Patient A. B. (Case 1) presented the bulbar hypoventilation syndrome in relatively "pure culture," that is, without gross irregularity of rate and depth and without incoordination of the respiratory muscles. Patient T. R. Q. (Case 2), however, exhibited what we anticipate may prove much more common, namely, gross irregularity of rate and depth (Fig. 1) as well as lowered sensitivity of the respiratory center to CO_2. It might well be that in other patients with bulbar involvement who show some irregularity and incoordination, this factor is also present to a significant extent, but the inadequate ventilation is attributed to the irregularity of the respiratory attempts rather than a lessening of the central respiratory drive, the diminished sensitivity of the respiratory center being masked by the more obvious motor dyskinesias.

The management of this situation is simple if the patient responds to verbal or gentle mechanical stimuli with increased ventilatory efforts. It is only necessary to watch him carefully, reminding him to breathe adequately when his center "forgets" to do so. If he does not respond adequately to such commands, he must, of course, receive some form of artificial respiration. Patient A. B. (Case 1) continued to lapse into his typical periods of hypoventilation with diminishing intensity for the subsequent 72 hours, the nurse in attendance reminding him to breathe each time. After that period, he appeared to breathe adequately. An electrophrenic respirator was kept at the bedside in order to provide for the possible emergency arising out of failure to respond adequately should that have occurred.

Patient T. R. Q. (Case 2), on the other hand, failed to respond adequately on two occasions, and artificial respiration was clearly indicated. The amount of fatigue induced in the patient by continued response to verbal commands (not to mention fatigue of the nursing personnel) must be estimated and weighed appropriately in any decision involving the question of whether or not to provide artificial respiratory support instead of verbal reminders. In retrospect, one cannot help but wonder if early implantation of the phrenic electrode and steadily maintained electrophrenic respiration during the critical period would not have conferred a more reasurring margin of safety in the management of this case. The concensus of the majority associated with patient T. R. Q. is that if presented with the same or a similar situation early electrode implantation is indicated. On the other hand, if patient A. B. (Case 1) had had an implantation it would have been superfluous since he managed quite well without it.

The spontaneous and readily induced fluctuations of the adequacy of respiration make it necessary to observe two precautions in the interpretation of blood gas data from these patients.

1. The blood must be drawn in such a way as to leave the patient undisturbed, since any stimulus sufficient to irritate the patient may produce an increase in ventilation of sufficient magnitude to produce normal

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blood gas values. It seemed to us that the best technique was to connect a three-way stopcock to the needle after it is inserted, connect the syringe, and flush it with saline. After at least five minutes, or when it is apparent that the respiratory disturbance resulting from the arterial puncture has abated, the handle of the stopcock is gently turned so as to empty a few drops of blood out the side of the three-way stopcock and then permit the blood to flow into the syringe.

2. There are spontaneous fluctuations in the adequacy of ventilation from hour to hour with no apparent relation to external stimulation. Data on blood obtained during the periods of more adequate ventilation would confer a false sense of security in the clinical management of the patient.

In view of these factors, it is important to realize that the obtaining of blood values indicative of hypoventilation is diagnostic of the hypoventilation syndrome in the presence of bulbar poliomyelitis but that normal blood values do not provide assurance of a normal respiratory center drive at times other than at that moment when the blood was drawn. The fact that normal values (Table 2) were obtained on the morning of the day (Aug. 29, 1950) when the near catastrophe

TABLE 2.—*Data on Patient T. R. Q.: pO_2 and pCO_2 in Arterial Blood of Patient with Respiratory Center Involvement Due to Bulbar Poliomyelitis*

Date, 1950	Sample	pO_2, Mm.Hg	pCO_2, Mm.Hg
Aug. 28	Spontanous respiration *	86.5	48
	Forced respiration †	105.5	38
Aug. 29	Spontaneous respiration	96.0	37

* Drawn five minutes after arterial puncture.
† Drawn after two minutes of forced respiration which immediately followed the drawing of sample 1.

occurred in patient T. R. Q. reveals the false sense of security that normal values can produce under these circumstances. In this case, the Aug. 29 blood sample was obtained immediately after the arterial puncture without regard for precaution 1 mentioned above.

Marshall and Rosenfeld [8] demonstrated that when the sensitivity of the respiratory center is depressed by barbiturates, the remaining activity of the center results largely from the hypoxic stimuli arising in the carotid and aortic bodies. For, by giving oxygen under these circumstances and thus removing the hypoxic stimulus, the already subnormal respiratory minute volume falls even further. The result is that the pCO_2 in the arterial blood, already at high levels, rises still further and may produce a secondary deepening of the respiratory center narcosis. This produces a state of affairs in which, even when the oxygen is stopped, spontaneous respiration may not be resumed since, at the level of carbon dioxide present, the center may then be refractory even to hypoxic stimuli.

It has been thought that the administration of carbon dioxide with oxygen under these circumstances would stimulate the lagging respiratory center to more adequate activity. We feel that there are two palpable objections to such a maneuver. First, the continued administration of carbon dioxide must of necessity produce a significant deviation from normal of the acid-base balance of the organism. Second, the administration of carbon dioxide to a patient with a slightly or moderately elevated arterial pCO_2 might well increase ventilation. However, if the patient's arterial pCO_2 already is elevated to the point where a further elevation will produce carbon dioxide narcosis and respiratory depression, it is apparent that the administration of carbon dioxide to such a patient is unwise.[9]

Since the urgent demands of the critical situation sometimes preclude precise analysis before initiating therapy, we feel that inhaled carbon dioxide under these circumstances might be hazardous.

Clinicians and physiologists are becoming increasingly aware that the abrupt administration of oxygen to an emphysema patient whose respiratory center has in some way become adapted to a high level of carbon dioxide (lowered sensitivity) can be hazardous.[10]

There are two practical implications of the above-presented data. First, there is the possibility that the respiratory center attacked by the poliomyelitis virus is depressed and that it may depend to a certain extent on the hypoxic stimulus for the level of its respiratory activity as described above. Since the care of such patients frequently includes the administration of oxygen, it is suggested that the precise determination of its effect on ventilation and arterial carbon dioxide levels is highly desirable. Should the administration of oxygen be accompanied with a decrease in ventilation, some form of artificial respiration is clearly indicated.

Secondly, while there is a reluctance on the part of a great many persons to treat the patient with bulbar poliomyelitis in the tank respirator, it is obvious that under these conditions some kind of respiratory support is required. As indicated by the sequence in the case of patient T. R. Q., the electrophrenic respirator may be of help under these circumstances, either alone or as a stopgap until the patient can be acclimatized to the tank respirator. Although making a prognosis of any kind in poliomyelitis is hazardous, at 1:30 a. m. on Aug. 30, when patient T. R. Q. was breathing at a rate of 0 to 4 respirations per minute and it was no longer possible to arouse the patient by verbal stimuli, it was clear that some sort of respiratory support was required if a catastrophe was to be avoided. In this episode, as in others of its kind, the brevity of the period of electrophrenic respiration required to re-establish a relatively normal sensitivity of the respiratory center was of considerable interest. One other patient, reported previously,[3] also responded in this manner after eight hours of electrophrenic respiration. It may be that the period of induced adequate ventilation breaks some vicious arc. The latter may be thought to consist of a series of events which impose a high pCO_2 and low pO_2 on the respiratory center, thus impairing its function and in turn producing an even higher pCO_2 and lower pO_2 to the point where carbon dioxide nar-

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9. Whittenberger, J. L., and Sarnoff, S. J.: Symposium on Specific Methods of Treatment; the Treatment of Respiratory Failure, M. Clin. North America **34**: 1335, 1950.

10. Marshall and Rosenfeld,[8] Comroe, J. H., Jr.; Bahnson, E. R., and Coates, E. O., Jr.: Mental Changes Occurring in Chronically Anoxemic Patients During Oxygen Therapy, J. A. M. A. **143**: 1044, 1950. Grandpierre, R.; Franck, C., and Lemaire, R.: L'action paradoxale de l'oxygène, J. physiol. **42**: 5, 1950.

cosis of the center occurs. The period of induced adequate ventilation reverses this pattern and partially restores the sensitivity of the respiratory center. The patient can then maintain himself until, because of some unknown factor, the sequence begins again. This line of reasoning will be recognized as highly speculative, since it may well be that an increased supply of oxygen to the medulla during adequate ventilation is responsible for restoring its sensitivity. It is, however, clear that the type of poliomyelitis patient described above may exhibit a severely diminished ventilation, which, if supported by artificial respiration for brief periods, may be a rapidly reversible state.

SUMMARY AND CONCLUSIONS

Diminished respiratory center activity, either with or without gross respiratory irregularity and incoordination, may occur in bulbar poliomyelitis. It is suggested that this results from an altered sensitivity of the respiratory center to carbon dioxide consequent to medullary involvement in this disease.

Verbal artificial respiration can be effectively administered under these circumstances if the patient is responsive and is observed continuously by competent personnel, and if it is not required for too prolonged a period.

This type of respiratory defect may occur more frequently than supposed, but may be masked by the more obvious abnormalities of breathing in bulbar poliomyelitis.

The possible hazards of oxygen administration under these conditions have been mentioned. These potenial hazards would, however, be readily overcome if any significant diminution of spontaneous ventilation is reversed by some means of artificial respiration.

Electrophrenic respiration may be of help under circumstances wherein spontaneous respiration is inadequate or becomes so following the administration of oxygen. It is obvious that at least one phrenic nerve must be uninvolved by the disease if electrophrenic respiration is to be used.

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INTRODUCTION OF BLOOD INTO THE PERITONEAL CAVITY

AN EXPERIMENTAL STUDY

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Intraperitoneal hemorrhage is frequently encountered on an active obstetric and gynecologic service. Therefore, correlation of quantity of free blood with resulting symptoms and with its fate represents information of considerable value to the clinician. For this reason whole blood and other similar materials varying in amounts were introduced at varying rates into the human peritoneal cavity.

SUBJECTS

Sixteen women about to undergo laparotomy formed the subjects of this study. Twelve were puerperal and awaiting tubal sterilization. Four had noninvasive, or intraepithelial, cervical carcinoma. Preoperative patients were chosen in order to afford opportunity for direct inspection during the subsequent operation. In addition, the protocols of three patients, each with accidental and massive intra-abdominal hemorrhage, were included. Essential data on these 19 patients are presented in the accompanying Table.

METHOD

Injections were made under local anesthesia through a 16-gauge needle inserted 2 to 4 cm. below the umbilicus and usually in the mid-line. Sometimes they were made in either the right or the left lower quadrant. Generally, whole blood was withdrawn from the patient's antecubital vein into a 20-cc. syringe, the barrel of which had been previously lubricated with mineral oil or melted petroleum jelly. The use of multiple syringes and two operators made it possible to inject as much as 500 cc. of whole blood at one time. Toward the end of the study, isotonic saline, plasma, and washed red blood cells were injected in a similar manner in some patients. The rate of injection varied with each patient and appeared to be a factor in the causation of various symptoms. Temperature and pulse rate were recorded carefully before injection, and afterward at hourly intervals for at least 12

Essential Data on Patients Included in Study

Patient	Age (Yr.)	Gravida	Para	Race	Preoperative Condition
C. S.	40	6	6	W	3 days puerperal
E. M. H.	31	8	8	N	13 days puerperal
H. Y.	29	7	7	W	4 days puerperal
M. L. R.	26	6	5	W	5 days puerperal
B. P.	41	4	4	N	9 days puerperal
V. M.	31	10	8	N	11 days puerperal
O. M. H.	38	10	8	N	7 days puerperal
A. P.	26	7	6	N	4 days puerperal
W. A.	25	6	6	N	59 days puerperal
M. E. W.	39	9	9	N	7 days puerperal
S. M.	48	15	14	W	4 days puerperal
E. T.	34	8	7	N	1 day puerperal
A. A.	22	4	4	N	Intraepithelial carcinoma of cervix
B. S.	27	5	5	N	Intraepithelial carcinoma of cervix
N. T.	25	6	5	N	Intraepithelial carcinoma of cervix
L. R.	21	2	2	N	Intraepithelial carcinoma of cervix
M. F. B.	23	1	0	N	Hemorrhage, omental vessel
C. L.	22	3	2	N	Ruptured ectopic pregnancy
H. W.	27	2	2	W	Ruptured spleen

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hours. White blood cell counts were made before injection, a few hours after injection, and on the following day. Blood was injected prior to operation so that we could know for certain that it was in the peritoneal cavity and could study its fate, as well as possible peritoneal reaction. In this series, in each of the 16 patients with a planned injection, the material was found within the peritoneal cavity. In a patient not included in the series, 330 cc. of whole blood supposedly injected intraperitoneally was totally lost. The blood was not found in the peritoneal cavity and did not appear in the stools, and there was no parietal hematoma or any soft tissue mass anywhere.

RESULTS

Naturally there were no definite end points, and evaluation of the experiments depended on the subjective observations and opinions of the observer and on the pain threshold and vocal response of the patient.

Following injection of less than 300 cc. of blood, the patient usually complained of fullness in the lower abdomen, and a desire to pass gas or belch. Some patients complained of uterine cramping or said the afterpains were intensified. Following injection of 300 to 550 cc. of blood, moderate to severe pain immediately ensued, gradually diminished, and disappeared after 15 to 30 minutes. However, if additional blood was injected, the pain recurred. Even when patients were unaware that additional fluid was injected, pain and discomfort were produced. This is one of the important findings of the study. Moreover, with each succeeding injection, symptoms could be evoked with decreasing amounts of fluid and tended to persist for increasing periods of time. Pain invariably disappeared within two hours after conclusion of injection. However, a few patients, when questioned closely, admitted a feeling of fullness in the lower abdomen at this time. Tenderness in response to deep palpation increased temporarily, but disappeared by the following morning. This was true even in patients who at operation were discovered to have as much as 500 cc. of bloody abdominal fluid.

Most patients were operated on within 24 hours of the initial injections. Approximately four-fifths of the injected blood was found remaining in the peritoneal cavity in each one. It was always liquid, and clots were seldom found in the patients in whom whole blood had been injected.

Five of the 16 patients received injections of materials other than whole blood. Five hundred cubic centimeters of isotonic saline solution was injected into one patient. The injection was begun rapidly, but, as with some of the other patients, was interrupted once or twice during its course. Pain appeared after about 200 cc. was injected. Subsequently, the pain could be reproduced with diminishing amounts of saline. When the abdomen was opened, there was merely a slight increase in the amount of intraperitoneal fluid. In other words, practically all of the saline was absorbed during 24 hours. This is entirely in accord with the experiments of Blackfan and Maxcy [1] reported in 1918.

Plasma was absorbed rapidly, but not so rapidly as isotonic saline solution. We employed Red Cross-prepared plasma. In one patient receiving 100 cc., pain developed, and at operation some peritoneal reaction was exhibited. A second patient received 475 cc. of plasma, and was found to have approximately 75 cc. of brownish fluid in the peritoneal cavity the next day. It seemed to the observer that there was proportionately more peritoneal reaction with plasma than with similar quantities of blood in other patients. However, this cannot be considered a valid observation since it was made on only one patient.

Two patients received red blood cells washed and resuspended in Ringer's lactate solution. In the patient receiving 260 cc., more than 100 cc. of bloody fluid was found at operation. In the patient receiving 520 cc., more than 300 cc. was found at operation. In other words, it would seem that because of the presence of the erythrocytes, rate of absorption of the Ringer's lactate solution was not so rapid as it might have been.

Pain could be produced with each of these materials, as well as with whole blood. In other words, it would seem that the intensity of the pain reaction, in addition to depending on the pain threshold of the patient, is roughly proportional to the quantity of injected material, rather than dependent on the composition of injected material. Experimental work by Capps and Coleman [2] in the human being suggests that localized pain results either from pressure on the parietal peritoneum with a stretching of the nerve endings in the subserosal layers, or from the tearing of the serosal cells with direct irritation to the subserosal nerve endings. Also, Capps and Coleman believe that abdominal rigidity is the result of reflex action from the irritated parietal peritoneum, or of an inflamed viscus in contact with parietal peritoneum.

Temperature elevations in excess of one degree Fahrenheit were not noted. Following injection of a large amount of fluid, a mild leucocytosis, sometimes to 19,000 cells per cubic millimeter, resulted within four to six hours but disappeared by the next day. At operation, the entire visible portion of the peritoneal surface was slightly injected, but no marked erythema or fibrin response was seen. No patient suffered any abnormal after-effect because of the injection.

REPORT OF TYPICAL PATIENTS

M. E. W. was seven days postpartum. After injection of 200 cc. of whole blood she complained of epigastric pain. She was placed in Trendelenburg position, but suffered no shoulder pain. After her restoration to horizontal recumbency, an additional 60 cc. of blood was injected; the epigastric pain recurred, but was practically gone at the end of an hour. At this time the patient complained of gas pains and stated that she felt better after passing gas. Following injection, no pulse change was noted and the temperature rise was insignificant. At the time of injection the white blood count was 12,800 per cubic millimeter. It was 15,600 four hours after injection and 9,200 twelve hours later, or 16 hours postinjection. During the night there was no difficulty, and at operation the next morning more than 200 cc. of liquid blood was found in the peritoneal cavity.

S. M. was four days postpartum. Red blood cells removed from 500 cc. of blood were washed and suspended in an equivalent amount of Ringer's lactate solution. Two hundred and fifty cubic centimeters of this washed blood cell suspension was injected during the course of 15 minutes. The patient complained of a feeling of fullness and a desire to defecate. These symptoms decreased, and after 15 minutes the injection was resumed with

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2. Capps, J. A., and Coleman, G. H.: Localization of the Pain Sense in the Parietal and Diaphragmatic Peritoneum, Arch. Int. Med. **30**:778-789 (Dec.) 1922.

an additional 120 cc. The discomfort reappeared, and actual pain was experienced for the first time. Nevertheless, when she was placed with the head down in moderate Trendelenburg position and remained there for five minutes, there were no symptoms of diaphragmatic irritation. After she had resumed the horizontal position, the injection was continued with another 75 cc. At this time marked discomfort with moderate to severe abdominal pain appeared. In other words, she had now received 445 cc. over a period of 40 minutes. Twenty minutes later another 55 cc. of washed cells produced definite pain, which disappeared during the next 30 minutes. At this time the symptoms were reproduced with 25 cc. Not only were they reproduced, but the patient now had really severe pain (chiefly in the epigastrium), fulness, and tenderness on gentle palpation. One and one-half hours after conclusion of the injection the pain had decreased so that there was only a slight tenderness in response to palpation and a minimal subjective sensation of fulness. Two hours after conclusion of the experiment the temperature was 98.6 F.; the pulse, 80 beats per minute; and the white blood count, 19,000 per cubic millimeter. Three hours after conclusion of the experiment the patient had no complaints and was out of bed and walking around the ward. At this time the white blood count was 12,700, the temperature was 99.4 F., and the pulse varied between 80 and 90 beats per minute. The following day more than 300 cc. of bloody fluid was found in the peritoneal cavity and the peritoneum was slightly injected. All conversation with the patient was through the medium of an interpreter, since the patient spoke no English. It was felt at the time that suggestion of ideas, from physician to patient, was minimized.

The following report is typical of a patient with accidental hemorrhage:

C. L., age 22, was in shock when first seen. At this time she complained of no pain. The abdomen was soft but there was moderate lower abdominal tenderness on deep palpation. She was found to have a ruptured right interstitial tubal pregnancy and there was nearly 3 L. of fluid blood with a few clots in the peritoneal cavity.

Apparently the general dulling of sensations of the patient with shock makes the symptoms and signs of abdominal pain and palpatory tenderness totally unreliable as a means of ascertaining the presence or absence of blood in the peritoneal cavity. Two other patients with massive accidental intraperitoneal hemorrhage exhibited similar symptoms; namely, absence of pain response and minimal tenderness on palpation. Nevertheless, one of them had 1,200 cc. of liquid blood in the peritoneal cavity; and the other, about 1,500 cc. Many other patients with subsequently proved massive hemorrhage were observed. All presented similar symptoms and signs, and their inclusion in this study would be unduly repetitious.

3. (*a*) Dorigo, A.: Richerche sperimentali sull'emoperitoneo, Policlinico (sez. chir.) **47**: 15-30 (Jan.) 1940. (*b*) Siperstein, D. M., and Sansby, J. M.: Intraperitoneal Transfusion with Citrated Blood, Am. J. Dis. Child. **25**: 107-129 (Feb.) 1923.

4. Sarason, E. L.: Cellular Reaction to Intraperitoneally Injected Blood, Yale J. Biol. & Med. **12**: 269-276 (Jan.) 1940.

5. Allen, L.: Peritoneal Stomata, Anat. Rec. **67**: 89-103 (Dec. 25) 1936.

6. Hahn, P. F.; Miller, L. L.; Robscheit-Robbins, F. S.; Bale, W. F., and Whipple, G. H.: Peritoneal Absorption, J. Exper. Med. **80**: 77-82 (Aug.) 1944.

7. Florey, H. W., and Witts, L. J.: Absorption of Blood from the Peritoneal Cavity, Lancet **1**: 1323-1325 (June 30) 1928.

8. Cunningham, R. S.: Studies on Absorption from Serous Cavities, Am. J. Physiol. **82**: 59-62 (Sept.) 1927.

9. Ponfick: Experimentelle Beiträge zur Lehre von der Transfusion, Virchows Arch. f. path. Anat. **62**: 273-335 (Jan.) 1875.

10. Cole, W. C. C., and Montgomery, J. C.: Intraperitoneal Blood Transfusion: Report of 237 Transfusions on 117 Patients in Private Practice, Am. J. Dis. Child. **37**: 497-510 (March) 1929.

COMMENT

Whole blood injected into the peritoneal cavity of experimental animals is harmless and produces almost no reaction.[3] Single injections caused no adhesions or evidence of peritoneal irritation. Massive coagulation did not occur, but there was slight microcoagulation. On the other hand, when multiple injections over a period of time were used in the rabbit,[4] hyperplasia of the connective tissue cells of the omentum and increased monocytic cell response of the peritoneal fluid were produced.

Frog erythrocytes injected into the peritoneal cavity of the white mouse [5] were absorbed intact, principally through the diaphragmatic lymphatics, although all of the peritoneal lymphatics are probably concerned with absorption. Hahn and others [6] confirmed lymphatic absorption in the dog, using radioactivated iron incorporated in the erythrocytes. Moreover, the red cells passed into the lymph spaces, vessels, and nodes without suffering injury or phagocytosis. The absorption of red blood cells is augmented by acceleration of the rate and depth of respiration and by increased intra-abdominal pressure.[7] However, the rate of absorption [6] varied in the dog from 20 to 100% in 24 hours.

Cunningham [8] observed that 10% aqueous dextrose solution was absorbed primarily by way of the blood capillaries of the rat and postulated that this must be the route of absorption of the fluid portion of peritoneally injected blood.

The therapeutic injection of blood into the human peritoneal cavity was performed as early as 1875 by Ponfick.[9] Since then, many have employed the method in acute and chronic primary and secondary anemia. More recently, Cole and Montgomery [10] injected 237 transfusions into the peritoneal cavities of 117 children. On the other hand, no study was found directly relating to the subjective reactions produced by the experimental introduction of blood into the human peritoneal cavity.

SUMMARY AND CONCLUSIONS

Sixteen women about to undergo laparotomy received injections of whole blood (11), saline (one), plasma (two) and washed red blood cells resuspended in Ringer's lactate solution (two). The records of three additional patients with accidental hemorrhage in excess of 1,200 cc. were included in the study in order to indicate the effect of massive amounts of intraperitoneal blood.

After injection of whole blood or resuspended erythrocytes, temperature elevation did not exceed one degree Fahrenheit. There was usually a transient leucocytic response, but in no instance more than 19,000 cells per cubic millimeter. By the day following injection there was usually a generalized peritoneal redness. About four-fifths of the total quantity of injected blood remained in a liquid state in the abdominal cavity. Clotting was invariably minimal.

From work done by others, it is known that red blood cells are absorbed chiefly by the lymphatics of the diaphragm, while the fluid portion of the injected blood enters the circulation by way of the blood capillaries.

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Following injections of less than 300 cc. of material, patients of this series complained of fullness in the abdominal cavity and a desire to belch and to pass gas. Such patients seldom experience true pain. When more than 300 cc. was injected, moderate to severe abdominal pain, depending on the emotional threshold of the patient, appeared at once, but in every instance was gone within two hours. On the other hand, tenderness in response to deep palpation sometimes persisted after this period of time. After the initial injection, it was possible to bring back the abdominal pain by small additional amounts of injected material. Translating this into clinical terms, it may be stated that in patients with suspected intra-abdominal hemorrhage, continuance of the complaint of fullness and pain indicates continuing or repeated hemorrhage. The pain response of the patient depends on her emotional threshold, and apparently on the quantity and not the character of the injected material. In three patients with massive accidental hemorrhage, the complaint of pain or fullness was conspicuously absent. Apparently the shock resulting from loss of quantities of blood into the peritoneal cavity dulls the sensorium, and therefore abolishes the reaction of pain.

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INACCURACY OF FOUR CHEMICAL PROCEDURES AS DIAGNOSTIC TESTS FOR CANCER

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During the past several years, interest in the chemical serodiagnosis of cancer has been revived by the introduction of several new procedures. Among these have been the methylene blue reduction time,[1] the heat turbidity index,[2] the Huggins iodoacetic acid index,[3] and the level of the mucoprotein fraction in blood.[4] Although none of the originators of these tests claimed them to be specific for the diagnosis of malignant disease, the suggestion has been made that some of these tests would be a definite aid in cancer diagnosis. The early evaluations of some of these tests indicated that they were fairly accurate. More recent studies on two of these procedures, however, have been rather discouraging.[5] It has been suggested that a battery of tests might prove to be more accurate than any one of its component parts. It has been the purpose of this study to compare the accuracy of the above tests run simultaneously on the same patients and to determine whether a battery of the four tests would give greater accuracy than any single test.

All patients were ambulatory and were referred for determination of suspected cancer or for therapy of an already diagnosed tumor. It was felt that such a series would provide the most rigid indication of the value of the tests from the point of view of practical cancer diagnosis. Both sexes and all age groups are represented. In the majority of cases, final diagnosis was made by biopsy.

Of 274 cases studied, there were 149 in which the diagnosis of cancer was ruled out, 77 in which the diagnosis of cancer was well established, and 48 in which there was doubt as to whether or not malignant disease was present at the time of the test. Data for the latter group are not included in this report. Many types of cancer were represented, including carcinoma of the breast, cervix, larynx, prostate, uterus, rectum and tongue, and malignant melanoma, basal cell carcinoma, and lymphosarcoma. The determinations were made by persons having no knowledge of the case histories.

METHODS

The blood samples were centrifuged within four hours of collection and the serum or plasma kept at refrigerator temperature (about 4 C.) until analyzed. The iodoacetic acid test was that of Huggins and his coworkers,[6] who used serum, the test being run within one week after the specimen was obtained. The end-points were read by the wire-loop technique and, to minimize variations in their reading, all tests were read by the same person. Total serum protein was determined by a biuret method.[7]

The methylene blue reduction time was determined by the method of Black [1b] (with use of 0.15% methylene blue, and the addition of caprylic alcohol to decrease foaming [8]). The test was run on plasma within 24 hr. after obtaining the specimen. The heat turbidity index obtained was that of Black and his colleagues [2] and was run on plasma within 24 hr.

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With few exceptions, all blood samples were obtained from three sources: the tumor board clinic of the Hollywood Presbyterian Hospital, Dr. S. Perzik, Beverly Hills, Calif., and Dr. S. Baker, Los Angeles.

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The mucoprotein in serum or plasma was determined by the method of Winzler and others [9] within two weeks after the specimen was obtained, a period over which this fraction is stable.

RESULTS

In the chart are bar graphs showing the distribution of results of the four tests for both groups, the values for individuals with cancer being shown by solid bars, and those for cancer-free patients, by open bars. No attempt was made in this evaluation to separate the cancer-free but diseased from normal patients, since the primary concern of this project was to evaluate the procedures as diagnostic tests for cancer. Actually, owing to the nature of the sources of test cases, very few "normal" cases were encountered. As seen from the bar graphs, there is a great spread with considerable overlapping for both groups in each test, although there is an unmistakable tendency for a shift when the group with malignant disease is taken as a whole.

The arbitrary values chosen to divide positive tests from negative ones were taken or estimated from the literature and were as follows: an iodoacetic acid index less than 9.0 was positive, and greater than 9.0 was negative; a methylene blue reduction time of more than 10 min. was positive, and of 10 min. or less was negative; a heat turbidity index greater than 96 was positive, less than 96 was negative; a mucoprotein value greater than 4.5 was positive, less than 4.5 was negative.

Two methods were used to evaluate the accuracy of the tests and of their combinations. The first of these, shown in column six, is the "over-all per cent accuracy" calculated by averaging the per cent accuracy of the two groups, those with cancer and those without cancer. The second method for expression of the data given in column seven is the Youden index or "J" value for the tests,[10] this value ranging from zero when there is no correlation of the test values with disease up to a value of unity when perfect correlation exists. This index has been recently criticized [11] on the basis that it does not take into account the "critical value" chosen to divide positive tests from negative, and that different "J" values can be obtained merely by changing the "critical value." "J" values, therefore, must be regarded as valid only for the "critical value" used in the test—i. e., the "critical value" chosen is considered part of the test. Inspection of the bar distribution graphs in the chart indicates that any increase in "J" values achieved by choosing different "critical values" could be only slight.

In the first four rows of Table 1 are given the results of the individual tests. Since no sharp lines of demarcation between positive and negative tests could be drawn for these data it was believed advisable to establish "doubtful" zones for each test around the arbitrary points dividing positive from negative. The zones arbitrarily chosen for these tests were as follows: iodoacetic acid index, 8.6 to 9.4; methylene blue reduction time, 9.75 to 10.5 min.; heat turbidity index, 90 to 100, and mucoprotein, 4.1 to 4.9 mg. per 100 cc. The correlation values for the four tests in which all values falling into these "doubtful" zones were discarded are given in rows five to eight, inclusive, of Table 1.

In Table 2 are given the statistics on the four tests used as a battery. In the first row are the results obtained when the battery is considered positive if at least one of the four tests is positive. Thus, out of 70 patients

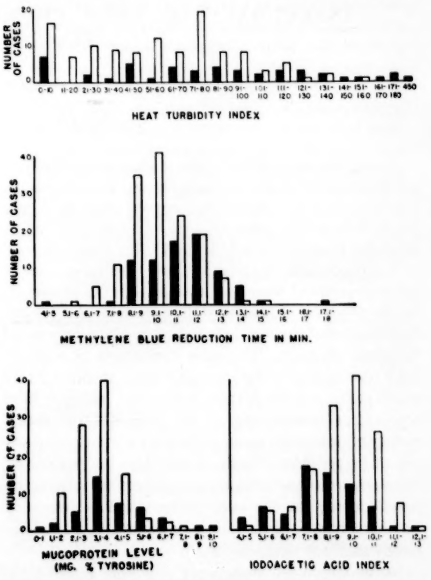

Chart showing distribution of test results among patients with cancer (solid bars) and without cancer (open bars).

with cancer, in 67 at least one of the four tests was positive; of 117 who were cancer-free, however, in 24 not even one test was positive. Likewise, in the second row, the battery is positive if two or more are positive, and, in the last row, if any three of the four are positive. Values falling in the "doubtful" zones were not discarded in these calculations.

The over-all per cent accuracy of the individual tests ranged from 61 to 69, and the "J" values lay between 0.2 and 0.4. The variation in the corresponding "J" values was not found to be statistically significant. As was expected, the "J" values tended to show an increase with the introduction of the "doubtful" zones although the individual increases were not statistically significant. If the battery of four tests was considered positive when one individual test or more was positive, it is seen that there

6. Huggins, C.; Miller, G. M., and Jensen, E. V.: Simplified Procedure for Serum Coagulation Test, Mimeo, 1949.
7. Weichselbaum, T. E.: An Accurate and Rapid Method for the Determination of Proteins in Small Amounts of Blood Serum and Plasma, Am. J. Clin. Path. **16**: Tech. Sec. (10): 40, 1946.
8. Stettner, M. M.; Baron, H.; Lowenstein, B. E.; Greenwald, A. E.; Mersheimer, W. L., and Kleiner, I. S.: A Clinical Evaluation of the Black-Kleiner-Bolker Blood Test for Malignant Disease, J. Lab. & Clin. Med. **35**: 136, 1950.
9. Winzler, R. J.; Devor, A. W.; Mehl, J. W., and Smyth, I. M.: Studies on the Mucoproteins of Human Plasma: Determination and Isolation, J. Clin. Invest. **27**: 609, 1948.
10. Youden, W. J.: Index for Rating Diagnostic Tests, Cancer **3**: 32, 1950.
11. Greenhouse, S. W.; Cornfield, J., and Homburger, F.: The Youden Index: Letters to the Editor, Cancer **3**: 1097, 1950.

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is a low percentage of false negatives but a high percentage of false positives. If the battery was considered positive when three of the four tests were positive the situation was reversed, namely, a high percentage of false negatives and a low percentage of false positives. When the battery was considered positive with a minimum of two tests positive, a balance between these two extremes was achieved, giving a higher over-all per cent accuracy and a significantly higher "J" value (significant by *t* test).[10] This "J" value is not, however, significantly higher than that of any of the individual tests employing the "doubtful" zones.

It is possible that such chemical tests for cancer might be more accurate for one type than for another. The only type of cancer sufficiently well represented in this series to warrant such an evaluation was that of carcinoma of the breast (20 cases). The iodoacetic acid index and the methylene blue reduction time were positive in 72 and 65% of the cases, respectively, in contrast to 69 and 66% for all types of cancer.

TABLE 1.—*Analysis of Results of the Four Chemical Diagnostic Tests for Cancer Given Individually*

Type of Test	Patients with Cancer: Total No.	Patients with Cancer: No. Positive	Patients with Cancer: Correctly Diagnosed, %	Patients Without Cancer: Total No.	Patients Without Cancer: No. Negative	Patients Without Cancer: Correctly Diagnosed, %	Weighted Over-All Accuracy, %	"J" Values
Iodoacetic acid index	65	45	69	136	75	55	62	0.24 ± 0.14 *
Methylene blue	77	51	66	144	93	65	65	0.31 ± 0.13
Heat turbidity	46	16	35	117	106	91	63	0.26 ± 0.15
Mucoprotein	41	14	34	99	86	87	61	0.21 ± 0.16
Values with Omission of "Doubtful" Zones								
Iodoacetic acid index	55	42	76	101	54	53	65	0.30 ± 0.15
Methylene blue	60	42	70	111	76	69	69	0.38 ± 0.17
Heat turbidity	42	15	36	112	101	90	63	0.26 ± 0.16
Mucoprotein	37	12	32	86	79	92	62	0.24 ± 0.24

* Twice the standard error and therefore the range giving 95% confidence.

TABLE 2.—*Analysis of Results of Battery of Four Chemical Diagnostic Tests for Cancer*

Results of Test	Patients with Cancer: Total No.	Patients with Cancer: No. Positive	Patients with Cancer: Correctly Diagnosed, %	Patients Without Cancer: Total No.	Patients Without Cancer: No. Negative	Patients Without Cancer: Correctly Diagnosed, %	Weighted Over-All Accuracy, %	"J" Values
1 or more positive	70	67	96	117	24	21	59	0.16 ± 0.09
2 or more positive	54	42	78	113	76	67	73	0.45 ± 0.14
3 or more positive	45	13	29	127	120	94	62	0.23 ± 0.14

COMMENT

As stated in the introduction, the early reports on these tests showed rather promising results. Calculating "J" values from the published data, 0.857 was obtained for the iodoacetic acid index,[5] 0.765 and 0.552 for the methylene blue reduction time and heat turbidity index, respectively,[9] and 0.700 for the mucoprotein level.[8] Later reports on the iodoacetic acid index yield "J" values of 0.161 and 0.233 [5b,c] which compare closely to the value of 0.244 obtained in the series reported here. It seems quite probable that the main cause for the apparent discrepancy between the earlier reports and the later ones, including the one presented here, is that the earlier ones dealt with patients hospitalized for cancer, who were therefore, on the average, further advanced, rather than ambulatory patients. This point has already been emphasized by Bodansky and McInnes.[5c] The "J" value of 0.700 for the plasma mucoprotein level calculated from the data of Winzler and Smyth [4] was in hospitalized cancer patients compared with normal individuals. The mucoprotein determinations in the present series, yielding a "J" value of 0.211, were performed in the same laboratory and clearly demonstrate the degree to which the extent of the cancer and the presence of other illnesses may cause overlapping of groups.

The accuracy of any one of the four tests reported on here is certainly not sufficient to warrant its classification as a diagnostic test for cancer. When the four tests are run as a battery and interpreted as positive if a minimum of two tests is positive, the accuracy is somewhat improved but still cannot be regarded as a diagnostic procedure. The idea of running a battery of such tests, however, has received some support here and deserves further consideration with other existing tests as well as with future tests.

The ideal diagnostic test gives neither false positives nor false negatives. In the statistical analysis used in this report both types of error are regarded as equally undesirable, although it is admitted that this is a debatable question.

CONCLUSION

The evaluation of four potential blood tests for cancer, the iodoacetic acid index, the methylene blue reduction time, the heat turbidity index, and the mucoprotein level have been carried out on ambulatory individuals with cancer or with nonmalignant diseases. Analysis of the results shows that these tests give correct results in only approximately 60 to 70% of the cases and thus cannot be regarded as accurate diagnostic tests for cancer. When the four tests are run as a battery and interpreted as positive if a minimum of two individual tests is positive, the correlation is slightly improved but still cannot be regarded as a test diagnostic of malignant disease.

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CLINICAL NOTES

ALLERGY TO PITUITARY CORTICOTROPHIC HORMONE

Samuel M. Feinberg, M.D.
Alan R. Feinberg, M.D.
and
Edward Bigg, M.D., Chicago

In view of the fact that the corticotrophic hormone (ACTH) is a protein, it is not surprising that hypersensitivity reactions to it would be encountered. Our early work on the repeated use of corticotrophin to prevent anaphylactic reactions in guinea pigs sensitized to horse serum indicated that the animals were being sensitized to corticotrophin. Our first experience with human sensitivity to corticotrophin is summarized in the following case report.

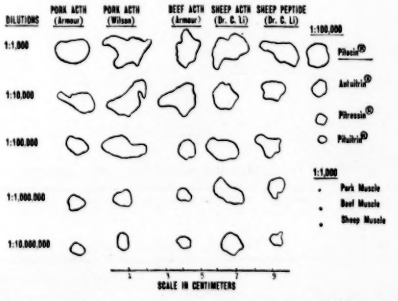
REPORT OF A CASE

F. J., a woman, 60, was admitted to Passavant Memorial Hospital in August, 1950, under the service of one of us (E. B.). Her major complaint was a crippling rheumatoid arthritis of about 20-years' duration. Cortisone was administered for 12 days, with some improvement in the arthritic symptoms. Because the improvement was not considered adequate, a course of corticotrophin therapy was planned. An injection of 25 mg. of corticotrophin (Armour) was followed within five minutes by alarming symptoms, consisting of generalized urticaria and angioneurotic edema, probable edema of the larynx, signs of asthma, and profound shock. After the injection of epinephrine and the use of additional measures, the patient recovered from this attack.

Inquiry elicited the following pertinent information. In the autumn of 1949 this patient had been treated at another hospital with corticotrophin. The first injection produced a mild urticaria. The injections were continued and the urticaria progressed. On the 12th injection the reaction was severer and was associated with angioneurotic edema and shock. The injections were then discontinued. No history of previous injections of pituitary products could be elicited. The personal or family history of allergy was not decisive.

Preliminary skin tests made with corticotrophin (Armour) about two weeks after the last constitutional reaction indicated a high degree of allergy to this substance. Subsequently, more complete studies were made. These are summarized graphically in the Figure. When corticotrophin solutions were injected intradermally in amounts of about 0.01 cc., whealing reactions were produced from dilutions as high as 1:10 million. Use of another corticotrophin of pork origin [1] prepared by somewhat different methods produced identical results. That this reactivity was not confined to the porcine corticotrophin was shown by the fact that use of beef corticotrophin [2] produced similar findings, and sheep corticotrophin [3] showed possibly even a greater reactivity. This cross reactivity was not due to any generic relation between the animals in question, since 1:1,000 dilutions of extracts of pork, beef, and sheep muscle injected intradermally were completely nonreactive. Of further interest is the fact that other pituitary preparations—anterior pituitary (antuitrin®), posterior pituitary (pituitrin®), vasopressin injection (pitressin®), and oxytocin injection (pitocin®)—also produced positive reactions. It was thought possible that a peptide preparation of corticotrophin might be free from allergenic properties. Use of a sheep corticotrophin peptide [3] also produced a high titer of skin reactivity. The skin of a normal subject was injected in several sites with the patient's serum. A positive passive transfer reaction was obtained to the porcine corticotrophin (Armour and Wilson). The other corticotrophin preparations produced false reactions in the 1:1,000 dilutions, while in higher dilutions no positive passive transfer test was obtainable. No positive transfer to the other pituitary substances was demonstrable.

The significance of allergy to corticotrophin is threefold. First, it is of practical importance because it must be taken into consideration as a hazard in this type of therapy. At the First Clinical ACTH Conference, several allergic reactions to this hormone were reported.[4] At the Second Clinical ACTH Conference, December, 1950, Brown and Hollander [5] described the reactions in seven patients (out of a total of 212 treated) with allergy to corticotrophin. In the discussion of that paper additional cases were cited by others.



Tracings of the wheals produced by the intradermal injections of corticotrophin and other substances in the patient. Note that the end point had not yet been reached with 1:10 million dilutions of corticotrophin. Attention is called to the entirely negative responses to tests with muscle extracts.

Second, it is of interest that a substance which is presumed to improve allergic manifestations is capable of giving allergic reactions. This seeming contradiction can be resolved when we realize that the action of corticotrophin is delayed and probably never adequate to prevent severe allergic reactions. The fact that a 12-day therapy with cortisone did not sufficiently modify the allergic reaction to an allergenic substance like corticotrophin obviously indicates that we should not depend on such agents to provide complete prophylactic measures against allergy.

Third, this case is of immunologic interest. In some of the patients of Brown and Hollander, beef corticotrophin did not produce skin reactions and was tolerated clinically. These were apparently examples of species specificity. The nature of the other reactions was not definitely stated, but it may be assumed that they were organ or corticotrophin specific. In our patient the specificity was related to corticotrophin or possibly to pituitary preparations in general. Further work would have to be done to clarify this point. It is interesting that our patient had an allergic reaction on the very first injection of corticotro-

From the Allergy Research Laboratory, Department of Medicine, Northwestern University Medical School, and Passavant Memorial Hospital.

1. Supplied by the Wilson Laboratories.

2. Furnished by The Armour Laboratories.

3. Supplied by Dr. C. H. Li, Department of Biochemistry, University of California.

4. Discussions of Traeger, C. H.; Forsham, P. H., and Markson, D., in Mote, J. R.: Proceedings of First Clinical ACTH Conference, Philadelphia, the Blakiston Company, 1950.

5. Brown, E. J., and Hollander, E. J.: Allergy to ACTH and the Use of Beef ACTH Proceedings of the Second Clinical ACTH Conference, Chicago, Dec. 9, 1950.

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phin. This is not in accordance with accepted immunologic principles and would suggest that this patient had previously received pituitary substances.

SUMMARY

An instance of severe allergic reaction to corticotrophin (ACTH) is described. The patient was allergic to all forms of corticotrophin in high dilution as well as to other pituitary preparations. The significance of the immunologic and clinical aspects of this subject is emphasized.

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DECUBITUS ULCER IN RHEUMATIC FEVER TREATED WITH CORTISONE

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and
Clayton R. Sikes, M.D., Atlanta

The increasing availability of cortisone and pituitary adrenocorticotropic hormone (ACTH) to the medical profession merits careful consideration of possible complications resulting from the use of these potent agents. The following case demonstrates the probable interference with normal wound-healing processes by cortisone.

REPORT OF A CASE

M. K., a Negro girl aged 13, was admitted to the medical service of Grady Memorial Hospital on Feb. 12, 1950, with the chief complaints of joint pain and fever.

Six weeks before admission she had noted a mild sore throat which lasted three to four days and then disappeared. Ten days before admission she experienced the onset of migratory polyarthritis, fever, anorexia, and occasional episodes of sharp precordial pain. She was confined to bed at home two days prior to admission and finally reported to the hospital because of increasing severity of joint pain.

Physical examination on admission disclosed a fever of 102 F., and diffuse swelling, heat, and exquisite tenderness over several joints. Cardiac examination revealed minimal enlargement, tachycardia, and apical protodiastolic gallop rhythm. No murmurs or pericardial friction rub were heard. Laboratory work revealed leukocytosis, and elevated sedimentation rate, but no evidence of the sickling phenomenon. An electrocardiogram was interpreted to be consistent with acute pericarditis.

The admission diagnosis was acute rheumatic polyarthritis and pancarditis, and the decision was made to treat her with cortisone. This medication was begun two days after admission, in doses of 100 mg. intramuscularly every 12 hr. Pain and tenderness associated with the polyarthritis were severe and were not controlled in spite of as much as 60 mg. of codeine by oral administration every four hours. Salicylates were not given. The slightest movement in bed caused extreme pain, and the patient voluntarily remained quiet and resisted any attempts to change her position. Six days after admission a dime-sized sacral decubitus ulcer surrounded by a small zone of necrotic skin was discovered. Thereafter she was moved from one side to the other at frequent intervals in spite of marked joint pain, and she was never allowed to remain on her back. The area of skin involved had never been the site of a cortisone injection.

One week after admission and five days after cortisone had been started, her rheumatic symptoms and fever were much improved. In another 48 hr. all evidence of polyarthritis had completely disappeared, and her temperature was normal. At this time the dose of cortisone was reduced to 50 mg. intramuscularly every 12 hr.

During the next week the patient felt quite well, and there was no return of rheumatic symptoms. However, the decubitus enlarged rapidly in spite of the absence of significant gross infection and every effort to prevent weight bearing on the area involved. At the end of the second week of cortisone therapy it became obvious that the enlarging decubitus was assuming more serious significance than the underlying rheumatic fever. No fresh granulation tissue was apparent, and gross infection from which colon bacilli were cultured was present. The diameter of the ulcer at the skin surface was 7 in. (17.8 cm.) and underlying tissues were involved down to the sacrum. Because of the postulated depression of mesenchymal tissue formation by cortisone and experimental data concerning wound healing, cortisone was discontinued and systemic antibiotics were begun. Five days later, adequate débridement was carried out, in addition to the measures which had been instituted when the decubitus was first discovered. The latter included protection of surrounding skin, moist dressings, and local antibiotics. Thereafter, healthy granulation tissue appeared, and normal healing progressed slowly but steadily.

Nine days after cortisone was discontinued, polyarthritis and fever reappeared, but an uneventful remission was produced with salicylates.

Total duration of hospitalization was four months, the last three of which were required for treatment of the decubitus. At the time of discharge it was thought that her rheumatic carditis had subsided.

COMMENT

Ragan and others [1] have demonstrated delayed healing in cortisone-treated rabbits, employing the techniques of surgical incision of the ear and experimental femur fracture. Subsequent microscopic examination revealed absence of the normal healing mesenchymal tissue response. Poor granulation tissue formation has also been noted in three patients while on pituitary adrenocorticotropic hormone therapy.[2] One patient with dermatomyositis exhibited delay in the healing of a biopsy incision. A second patient being treated for disseminated lupus erythematosus demonstrated failure of two abscess drainage incisions to heal while pituitary adrenocorticotropic hormone was continued and prompt appearance of healthy granulation tissue after it was discontinued. In a third patient a decubitus ulcer developed, similar to the one reported here, while under treatment for lupus. Again, the well-recognized weakness of supporting tissues in Cushing's syndrome is worth recalling.

In this case the decubitus ulcer probably appeared because of pressure necrosis of the skin, secondary to severe polyarthritis and immobilization during the first five hospital days when cortisone was ineffective in alleviating the exquisite joint pain and tenderness. Since the relief of joint pain in acute rheumatic fever by cortisone may require as long as four to seven days, in the future we shall use salicylates in addition to cortisone when the expected beneficial results from the latter are delayed as in this case. It is believed that this case merits attention because of the rarity of decubiti in well-nourished young persons and the possible relationship to cortisone. It seems unlikely that cortisone directly produced the lesion, but the early rapid increase in size in the relative absence of gross infection and the failure of granulations to appear in spite

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From the Medical Service, Grady Memorial Hospital, and the Department of Medicine, Emory University School of Medicine.

Cortisone used in this case was purchased by the Georgia Heart Association as part of a grant for the study of rheumatic fever.

1. Ragan, C., and others: The Effect of ACTH and Cortisone on Connective Tissue, Bull. New York Acad. Med. **26**: 251, 1950.

2. Ragan, C.; Grokoest, A. W., and Boots, R. H.: Effect of Adrenocorticotrophic Hormone (ACTH) on Rheumatoid Arthritis, Am. J. Med. **7**: 741, 1949.

of heroic local measures were quite probably secondary to a cortisone inhibitory effect upon the normal wound-healing process.

SUMMARY

A sacral decubitus ulcer developed soon after cortisone treatment was initiated in a case of acute rheumatic fever. The rapid increase in size of the decubitus and failure of all local measures to induce healing were attributed to suppression of the normal wound-healing mechanism by cortisone. Further use of this drug after the development of such a complication would seem inadvisable. It is recommended that salicylates be used in addition to cortisone in the presence of severe polyarthritis.

Grady Hospital.

ACTIVE RHEUMATIC FEVER DURING PREGNANCY

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and
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Active rheumatic fever occurring during pregnancy is rare. Hamilton and Thomson [1] found seven authentic cases of recurrent rheumatic fever in 781 pregnant women with chronic rheumatic heart disease. This represented 700 patient-years of study. These authors further state that they "made the diagnosis with more or less certainty only ten times in twenty years of extraordinary opportunity."

The following case is reported in order that experience in the management of this complication may be gained.

REPORT OF CASE

H. R., a Negro female, had had no significant illnesses until she was 14 years old, when there was pain in the left foot and ankle for approximately one week. She was then apparently well until age 18, when she became ill, having a painful, swollen right wrist, and fever. As the wrist improved the fingers and knees became painful but not swollen. She was treated at home with acetylsalicylic acid and was well after three weeks. No mention of heart involvement was made to her.

Again she was well and able to work until age 21, at which time she entered Morrisania City Hospital with migratory polyarthritis, fever, a soft systolic murmur at the apex of the heart, and a coarse systolic murmur noted at Erb's point. The sedimentation rate was 24 mm. in 30 minutes. P-R intervals varied from 0.22 to 0.24 sec. and the QT complex was 0.434 sec. The S-T segments were slightly elevated in leads 1, 2, and CF_4. The initial blood pressure of 164/84 fell to 140/80 after bed rest. Hemoglobin value was 65%; red blood count 3,400,000; white blood cell count 23,000, with 82% polymorphonuclear cells and 18% lymphocytes. She responded to salicylate therapy and was sent home after three months. The final diagnosis was inactive rheumatic heart disease and mitral insufficiency. Fluoroscopy was not done.

At age 23 she had an uncomplicated pregnancy with spontaneous delivery of a normal girl, weighing 6 lb. 5 oz. (2.8 kg.), after 13½ hours of labor. Postpartum one observer noted systolic and presystolic apical murmurs. The urine on two occasions showed albumin. No electrocardiograms were taken.

From the Prenatal Cardiac Clinic (Dr. Horowitz, Chief) and the Department of Electrocardiography, (Dr. Burstein, Director), Morrisania City Hospital.

1. Hamilton, B. E., and Thomson, K. J.: The Heart in Pregnancy and the Childbearing Age, Boston, Little, Brown & Company, 1941.

She was next hospitalized the following year, on Feb. 13, 1949, because her right knee had been hot, painfully swollen and tender for 24 hours. Her menstruation had previously been regular, and because she had missed her last two periods she believed she was pregnant (the last menses was on Nov. 26, 1948). Two weeks previously cardiac fluoroscopy, performed in the outpatient department, revealed enlargement of the left auricle, and of the inflow and outflow tracts of the left and right ventricles. The electrocardiogram at that time gave a rate of 92 per minute, P-R interval 0.24 sec., and the QT complex 0.496 sec.

The patient was a markedly obese, normally developed Negro woman, 24 years old, not too distressed except for pain around her right knee joint which was hot, swollen, tender, and reddened. Her temperature was 101 F.; pulse regular at 110 per minute, and respirations 26 per minute. Blood pressure was 130/70. There was no dyspnea, cyanosis, clubbing of fingers or toes, or peripheral edema. The neck veins were not distended. No skin nodules, rash, or enlarged lymph nodes were observed. The lungs were clear. The liver edge was not palpable. The heart was not enlarged to percussion; the point of maximal impulse was in the sixth left interspace within the midclavicular line. Sounds were rapid, rate 110 per minute, regular, and of good muscular quality. No thrills were felt. Mitral first sound was not accentuated. A harsh apical systolic murmur was transmitted to the aortic area. P_2 was greater than A_2. Pelvic examination was omitted. Hemoglobin value was 70%; white blood count was 13,500, with 78% polymorphonuclear cells and 22% lymphocytes. Sedimentation rate was 30 mm. in 30 min. Repeated blood cultures were normal, as was the serologic study. Electrocardiogram showed a sinus tachycardia, rate 120 per minute, P-R interval 0.26 sec., and QT complex 0.460 sec. Urinalysis revealed no abnormality. The Aschheim-Zondek test (for pregnancy) was positive.

The second day after admission the left knee and both ankles became swollen and tender. She was treated with acetylsalicylic acid, 8 gm. (120 grains) daily in divided doses. Within 24 hours all signs and symptoms referable to the joints had disappeared. She remained comfortable although tachycardia of 100 to 120 per minute and a low grade fever (100 F.) persisted. Digitalis leaf, one cat unit daily, had been given from admission until March 10. Salicylates had been stopped on March 4. Occasional extrasystoles of ventricular origin were noted. P-R interval continued at 0.26 sec. and a second stage conduction block was manifest in the electrocardiogram of March 7. Opinion was divided regarding interruption of pregnancy, and thus the patient continued the second trimester.

Suddenly, on March 18, the 33rd hospital day, the temperature rose to 103 F. and the pulse was regular at 160 per minute. The patient was extremely apprehensive, dyspneic, sweating profusely, and coughing pink, frothy sputum. Blood pressure was 186/86. Medium moist rales were present at both lung bases. The electrocardiogram revealed a sinus tachycardia, rate 150 per minute, the P waves were buried in the T waves, and the QT complex was 0.569 sec. She was treated with oxygen, morphine, mercurial diuretics, and penicillin. At this time the clinical impression was either acute left ventricular failure, pulmonary embolus, or bronchopneumonia.

Next day the temperature remained at 103 F.; pulse 144 per minute, regular; blood pressure 130/80. The basal rales had cleared. The neck veins were not distended. The heart sounds were muffled at the apex. The liver edge was not palpable. There was no evident phlebitis, calf tenderness, or Homan's sign. By the following day the temperature dropped to 100 F. and the patient both felt and looked better. After two days oxygen and penicillin were discontinued. However, the signs of rheumatic activity persisted: the temperature near 100 F.; elevated sedimentation rate (24 mm. in 30 min.); increased P-R interval (0.26 sec.), and tachycardia of 100 per minute. Again staff opinion was divided on interruption of pregnancy, so the patient was allowed to proceed to term.

During the latter part of March, systolic and diastolic murmurs were heard at the base in addition to the apical systolic murmur previously present. Blood pressure was 180/50. It was believed that aortic insufficiency could now be diagnosed definitely. Since rales were heard occasionally at the lung bases on

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March 30, the patient was started on digitoxin and digitalized during the next three days. She was maintained on 0.1 mg. daily thereafter.

She felt so much better on this regimen that she asked to return home. She was therefore placed under the supervision of the Home Care Department on May 3, her 79th hospital day, and was visited by a medical resident physician each week. On May 18, she was brought to the hospital for an electrocardiogram which showed a rate of 120 per minute, P-R interval 0.20 sec., QT complex 0.465 sec., diphasic T in leads 1, 2, and CF_4, and depressed S-T segments in leads 1 and 2. The sedimentation rate was 30 mm. in 15 min.

The following day she was markedly orthopneic and showed edema about the ankles. Numerous moist wheezes were present. The liver was tender to palpation and was found 3 fingerbreadths below the right costal margin. On direct questioning the patient admitted that she had not taken any digitalis after her discharge from the hospital 16 days previously. She was immediately given digitoxin and meralluride (mercuhydrin®), and kept at bed rest, and once again she responded.

Spontaneous rupture of the membranes occurred on May 21. She was again hospitalized, continued on digitoxin 0.2 mg. daily, and 2 cc. of meralluride twice weekly. She was quite comfortable on bed rest; all signs of failure cleared. Electrocardiogram on June 1 revealed a rate of 100 per minute, P-R interval 0.24 sec., and QT complex 0.460 sec. The obstetric consultant stated that interruption of pregnancy was not warranted at this time.

She was permitted to return to the home care service on June 3, and remained on complete bed rest with digitoxin and mercurials, as before, with no signs of failure. About 8 a. m. on June 28 spontaneous labor began; this was about the seventh month of pregnancy. Because of an outbreak of diarrhea in the nursery, the patient was transferred to another city hospital for delivery.

Within several hours the patient became markedly orthopneic and apprehensive. Her temperature rose to 101 F., pulse to 160 per minute (regular), respirations to 60 per minute, and the blood pressure to 240/70. Rales were present at both lung bases, the neck veins were distended, the liver edge was down 2 fingerbreadths, and the ankles were edematous. The heart was enlarged both to left and right; mitral systolic and diastolic and aortic diastolic murmurs were audible.

She was treated with continuous oxygen by mask, morphine, intravenous mercurial injections, and 1.6 mg. lanatoside C ("cedilanid") intramuscularly. Her condition deteriorated steadily. By 7:30 p. m. the cervix was completely dilated. She was given a saddle block anesthesia and was easily delivered by low forceps of an apparently normal 3 lb. (1.3 kg.) male infant. During the procedure she was given oxygen continuously and kept in high Fowler's position. She seemed to improve for a short time after delivery, but despite therapy her failure increased and she died at 5:35 a. m., 10 hours and five minutes after delivery. Gradual respiratory embarrassment developed in the infant and he died 13 hours and 15 min. after birth.

Permission for post-mortem examination was not obtained.

COMMENT

The presence of active rheumatic carditis in pregnancy poses problems to both the internist and obstetrician. First, the diagnosis of activity must be established, and second, a course of action must be determined. During pregnancy it may be especially difficult to decide on the presence of activity; and, since this complication occurs so rarely, sufficient experience has not been accumulated to establish criteria for its management.[2]

It should be emphasized that during a normal pregnancy new systolic murmurs may appear as well as a low grade fever, leukocytosis, elevated sedimentation rate, and vague joint pains. Diseases such as sickle cell anemia, lupus erythematosis, and rheumatoid arthritis, must be differentiated. In order to make a definite diagnosis of acute rheumatic fever, Jones [3] requires the presence of at least one major and two minor criteria. Sokolow and Snell [4] state "the diagnosis of carditis, . . . has depended largely on significant transient electrocardiographic changes, particularly partial auriculo-ventricular block and inverted T waves in Leads 1, 2, and 4, alone or in combination. Other objective evidences of carditis have been less frequently observed." Taran [5] believes that electrocardiographic changes are most sensitive indicators of rheumatic activity. Pardee [6] notes that sometimes in the electrocardiogram only was there any sign of rheumatic activity to be found.

The question of the invariable presence of carditis in every case of acute rheumatic fever remains. Sheehan and Sutherland [7] believe that in any pregnant chronic rheumatic cardiac patient recurrent endocarditis may develop without any recognizable exciting cause other than the pregnancy itself. In none of their cases were Aschoff bodies found, but this in itself does not exclude a diagnosis of rheumatic carditis.[8] McKeown [9] describes the findings in six pregnant rheumatic cardiac patients with mitral stenosis who died in congestive failure. Of these, four had rheumatic vegetations and Aschoff bodies of recent development in the myocardium. One patient had subacute bacterial endocarditis with myocardial Aschoff nodules. In only one was there complete absence of any evidence of recent rheumatic carditis.

Active rheumatic fever lingers a variable length of time under present medical management. The use of corticotrophin (ACTH) or cortisone gives promise of stopping the rheumatic infection.[10] Until these substances become more generally available, the presence of a smouldering rheumatic carditis plus the load of pregnancy weights the balance toward congestive failure and possibly death.

Cohen and Thomson,[11] and more recently Hamilton,[12] and Palmer and Walker [13] have shown by means of cardiac catheterization studies that the cardiac output in normal pregnant women increases gradually from the

2. Hamilton and Thomson.[1] Bramwell, C., and Langson, E.: Heart Disease and Pregnancy, London, Oxford University Press, 1938. MacKenzie, J.: Heart Disease and Pregnancy, London, Oxford University Press, 1921. Jensen, J.: The Heart in Pregnancy, St. Louis, C. V. Mosby Company, 1938. Schaeffer, A.: Berl. klin. Wchnschr. **23**: 79, 1886. Hefferman, E. B.: Rheumatic Fever Complicating Advanced Pregnancy, M. J. Australia **1**: 608, 1922. Hollander, A. G., and Goldsmith, J. W., Jr.: Acute Rheumatic Fever Complicating Advanced Pregnancy, Am. J. Obst. & Gynec. **42**: 333, 1941.

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12. Hamilton, H. F. H.: The Cardiac Output in Normal Pregnancy as Determined by the Cournand Right Heart Catheterization Technique, J. Obst. & Gynæc. Brit. Emp. **56**: 548, 1949.

13. Palmer, A. J., and Walker, A. H. C.: The Maternal Circulation in Normal Pregnancy, J. Obst. & Gynæc. Brit. Emp. **56**: 537, 1949.

10th week. A maximum level, about 26% above the nonpregnant state, is reached between the 26th and 29th weeks, after which there is a slight fall. From the 38th week there is a marked fall in cardiac output almost to nonpregnant levels which continues through the puerperium.[12]

Therefore, if a pregnancy is to be interrupted for cardiac reasons, this must be done as early as possible before the sixth lunar month. Until the third lunar month this may be accomplished by a dilatation and curettage. Afterward an abdominal hysterotomy must be performed. Unless there are compelling obstetric indications, interruption should not be attempted after the sixth lunar month. The cardiac load is reaching its maximum.[14] The additional strain of an abdominal operation on the overburdened heart may cause failure and death. Furthermore, toward term the cardiac burden of pregnancy falls markedly.[12]

In the patient discussed here, three definite episodes of acute rheumatic fever occurred before the final pregnancy. In the second month of pregnancy, two weeks before hospitalization, the electrocardiographic demonstration of an increased P-R interval, 0.24 sec., and a QT complex of 0.496 sec. indicated another episode of active carditis which waxed and waned throughout the pregnancy and ended in the death of mother and infant. Interruption in the first trimester was withheld because she seemed to improve. Unfortunately, during the early part of the second trimester she went into congestive failure but passed the sixth lunar month before interruption was again feasible. She went into spontaneous labor during the seventh month while the cardiac burden was at its maximum. Death of the mother and infant followed within the first day postpartum.

Thus, in the presence of active carditis, early interruption of the pregnancy might have saved the life of the patient. The rheumatic fever would have been treated in the usual manner and, statistically, her chances for recovery from the acute carditis would have been excellent.[15]

SUMMARY AND CONCLUSIONS

A case of active recurrent rheumatic fever with carditis beginning before the second month of pregnancy, and ending in the death of both mother and infant during the seventh month, is described.

From a study of the pertinent literature and our experience with this patient we believe that when active rheumatic carditis is diagnosed pregnancy should be terminated as early as possible before the sixth lunar month. Since the cardiac burden of pregnancy reaches its maximum after this time, interruption by an abdominal operation imposes an additional load which may cause failure and death. In the last trimester the patient should be permitted to go to term, unless obstetric complications supervene, in the expectation that the physiological decrease in the cardiac load after the 38th week of gestation will change the prognosis.

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14. Cohen and Thomson[11]; Hamilton,[13] and Palmer and Walker.[13]

15. Levine, S. A.: Clinical Heart Disease, Philadelphia and London, W. B. Saunders Company, ed. 3, 1945.

THROMBOCYTOPENIC PURPURA IN PREGNANCY

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In 1948 Barnes and Doan [1] found only six authenticated cases in the literature of thrombocytopenic purpura complicating pregnancy in which splenectomy was done; to this series they added two cases of their own. In the literature there is still uncertainty regarding the influence of pregnancy on the indications for splenectomy, and our purpose in presenting a ninth case is to attempt to assist in resolving this problem.

REPORT OF A CASE

B. D., a 24-yr.-old Negro woman, had a history, which dated back to early childhood, of easy bruising and of prolonged bleeding following injury. Two years prior to admission she had bled profusely after a tooth extraction, and 18 mo. prior to admission she had had a prolonged and profuse menstrual period diagnosed by a clinic physician in another hospital as a spontaneous abortion; however, her menses immediately prior to this episode had been regular, and the physician had made no pelvic examination or performed a curettage.

She was seen in the third month of her second pregnancy; the first had gone uneventfully to term five years before, and the child is living and well except for bronchial asthma.

At the first examination her hemoglobin content was 7 gm. per 100 cc., and, despite therapy with iron for three months, it never rose above 8 gm. per 100 cc. Throughout her pregnancy her gums bled easily when she brushed her teeth, and in the sixth month of her pregnancy a generalized petechial eruption developed.

Physical examination findings were normal at this time, except for those incident to her pregnancy and evidence of bleeding at the sites mentioned. The spleen was not felt. Laboratory findings included a bleeding time of seven minutes, normal clotting time, 90,000 platelets per cubic millimeter of blood, and a normochromic anemia with a hemoglobin content of 8 gm. per 100 cc. The percentage of reticulocytes, the prothrombin level, and the white cell count and differential count were normal. There was no clot retraction in 24 hr.

The patient deteriorated rapidly, both from a hematologic and clinical standpoint. The platelet count fell progressively to 5,000 per cubic millimeter of blood. Protamine sulfate was given intravenously because of the finding of increased heparin tolerance, but new petechiae appeared and a hemorrhage into the urinary tract developed. Bone-marrow aspiration showed all elements, including megakaryocytes, to be normal.

The patient was given a transfusion and splenectomy was done. Technical difficulty was encountered because of the large uterus; despite double ligation of the splenic pedicle, there was troublesome bleeding owing to the tearing of adhesions between the spleen and the parietal peritoneum.

Postoperatively the rise in the platelet count was disappointing, reaching a maximum of 50,000 per cubic millimeter of blood by the sixth postoperative day. There was bloody drainage from the operative site. The blood pressure was at shock level for two hours following the operation, and fetal heart sounds were not heard after this time.

On the seventh postoperative day, while still showing clinical evidence of active thrombocytopenic purpura, the patient was delivered of a stillborn macerated fetus with a blood loss of less than 150 cc. from the placental site.

During the following three days the patient became increasingly icteric and had daily hematemesis. A presumptive diagnosis was made of splenic vein thrombosis. On the 12th postoperative

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day the patient had a massive hematemesis; she died the following day in shock and semicoma, despite transfusions, oxygen, and other supportive therapy.

COMMENT

Pregnancy complicating thrombocytopenic purpura may modify the therapeutic approach with regard to the liability, if any, of these patients to exsanguinate from the placental site, the liability to premature separation of the placenta, and the liability of the newborn infant to be thrombocytopenic, if the mother is in relapse at the time of delivery.

At first glance it would appear obvious that a patient with hemorrhagic tendencies would be likely to hemorrhage severely from the placental site. Several reports in the literature have supported this view, notably, those of Mosher [2] in 1923 and of Rushmore [3] in 1925. Mosher states, "Nearly all cases of purpura hemorrhagica which go to term end fatally at delivery or soon after labor from hemorrhage." The evidence presented, however, is not convincing. The majority of the 44 cases presented are culled from the literature of the 19th century, and clear differentiation is not made between idiopathic thrombocytopenic purpura, symptomatic purpura, and hemorrhagic states associated with scurvy and pregnancy toxemia. Eleven of the cases are abstracted, and the stated cause of death in nine of these is not hemorrhage from the placental site. Rushmore also reports (in 1925) a high maternal mortality in cases collected from the literature, probably including many of those reported by Mosher two years earlier. Case reports are not offered in support of his statements.

On the other hand, there are those authors who feel that thrombocytopenic purpura, even in relapse at term, does not increase the liability to postpartum hemorrhage. Barnes [4] observed that postpartum blood in normal patients does not clot spontaneously unless seeded by blood from a cervical or vaginal tear. He collected postpartum blood in normals from the cervical os and found that it behaved like defibrinated blood. He concluded that the cessation of uterine bleeding depends only to a minor degree on hematologic factors and to a much greater degree on the closing of uterine sinuses by muscular contraction. This view has been supported clinically by McGoldrick and Lapp,[5] who collected from the literature 76 cases of leukemia in pregnancy. Of these only three died of postpartum hemorrhage, and two of the three had adequate obstetrical causes to explain the bleeding. Burnett and Klass [6] in 1943 found in the literature only four authenticated cases of thrombocytopenic purpura in pregnancy; they added a fifth of their own. Of the five cases, two delivered while in spontaneous remission; one delivered without excessive blood loss, although in relapse at the time and bleeding excessively from other sites; one had splenectomy intrapartum with remission, and one died of postpartum hemorrhage. Polowe [7] did a splenectomy intrapartum with remission; the patient went normally to term. Finn [8] delivered two previously splenectomized patients in relapse; neither bled excessively.

It is difficult to assess the incidence of placental separation in these cases, since the only large series reported are those which had not received diagnosis that was sufficiently critical.

It appears established that infants of thrombocytopenic mothers in relapse at the time of delivery may be themselves thrombocytopenic. Finn [8] reported a thrombocytopenic infant in one of his two cases; Burnett and Klass [6] reported a case of hemorrhagic disease in the infant, although blood studies were not done, and Wintrobe [9] reported an additional case.

In summary, a case has been presented of a woman with typical thrombocytopenic purpura who failed to respond clinically or hematologically to splenectomy in the course of pregnancy. Nevertheless, she was delivered of a stillborn fetus a few days postoperatively without excessive blood loss. This is in conformity with one school of thought found in the literature. As a postmortem was not permitted, we only can speculate that this patient's failure to respond may have been caused by the presence of an accessory spleen.

We feel that patients with thrombocytopenic purpura in pregnancy should be evaluated for splenectomy according to the usual indications and contraindications and without reference to the presence of the fetus.

Dr. Isadore Rothstein and Dr. Ira Miller, of the Department of Pathology, assisted in the hematologic studies.

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HOMOTRANSPLANTATION OF THE KIDNEY IN THE HUMAN

SUPPLEMENTAL REPORT OF A CASE

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Successful homotransplantation of human tissue is a subject of great interest to the medical profession. Because widely diversified and conflicting theories still exist as to the efficacy of this procedure (since most of the important experimental work has been done on laboratory animals and the results may not always be similar in man), and inasmuch as these conflicting views have led to an attempt to evaluate homografting in man, this study was made.

2. Mosher, G.: Complication of Purpura with Gestation, Surg., Gynec. & Obst. **36**: 502 (April) 1923.

3. Rushmore, S.: Purpura as a Complication of Pregnancy, Am. J. Obst. & Gynec. **10**: 553 (Oct.) 1925.

4. Barnes, A. C.: Postpartum Blood: Its Clotting Mechanism and Relation to Peripheral Blood Picture, Am. J. Med. Sc. **213**: 463 (April) 1947.

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6. Burnett, C. W. F., and Klass, I.: A Review of the Problem of Purpura During Pregnancy, J. Obst. & Gynaec. Brit. Emp. **50**: 393 (Dec.) 1943.

7. Polowe, D.: Splenectomy in Pregnancy Complicated by Thrombocytopenic Purpura Hemorrhagica, J. A. M. A. **124**: 771 (March 18) 1944.

8. Finn, W.: Thrombocytopenic Purpura in Pregnancy: Review of the Literature with Report of 3 Cases, Am. J. Obst. & Gynec. **48**: 497 (Oct.) 1944.

9. Wintrobe, M.: Clinical Hematology, Lea & Febiger, 1949, p. 618.

The preliminary report of this case appeared in THE JOURNAL, Nov. 4, 1950.[1] Therein it was reported that the operation took place on June 17, 1950. At that time a kidney from a woman of approximately the same age, blood type, and Rh type as the patient was transplanted to the renal pedicle of the patient after the removal of a polycystic left kidney. An end-to-end anastomosis of the renal vessels and ureter around a catheter was done, and the blood supply to the grafted kidney was noted to be re-established. The postoperative course was essentially uneventful, and by the third postoperative day the urinary output was observed to exceed total fluid intake by 1,750 cc.; this urinary output diminished to the normal level in relation to total intake by the 14th postoperative day. Experimentally, it has been shown that transplanted kidneys sometimes excrete more than twice the amount secreted by normal kidneys for a short time following transplantation.[2]

SUPPLEMENTAL REPORT OF A CASE

On the 52nd postoperative day indigo carmine dye was observed to emerge from both ureters following parenteral injection. Ten days later (the 62nd postoperative day) a retrograde injection of contrast medium on the grafted side revealed an incomplete stricture of the ureter. A small amount of the dye was observed by x-ray to pass upward beyond the site of the obstructive stricture. On the 63rd postoperative day an exploratory operation through the original flank incision showed the kidney to be normal in size and consistency. It was living, and the blood supply from the renal vessels was present. Repair of the ureteral stricture was deferred because of the presence next to the kidney of a small abscess 3 by 3 cm., which was probably due to fat necrosis and did not involve the homograft. This abscess was drained and the wound was closed in 10 days.

The general health of the patient continued to be excellent, results of her blood chemistry studies and urinary output being within the normal range (nonprotein nitrogen of Jan. 25, 1951 was 35 mg. per 100 cc.). It is believed by us that the progressive ureteral stricture gradually greatly diminished the urinary output.

On April 1, 1951, the patient was again operated on through the original incision. The homograft had diminished in size from that of a normal kidney to approximately 4 by 3 by 2 cm. The ureteral and pelvic structures were absent, but the sutures disclosed the site of the original ureteral anastomosis. The blood supply was still present. The tissue itself was not enveloped in fibrous tissue; it was brownish-red, similar in color to normal kidney tissue, and still definitely alive but apparently not producing urine.

The reports of Servelle and others [3] in Paris in THE JOURNAL, May 26, 1951, reveal three cases, in each of which kidney function has been observed following homotransplantation to the iliac vessels with a cutaneous ureterostomy.

One of us has had personal communication with Drs. Kuss and Tienturier [4] at the Hospital of Paris, who state that they have completed 16 kidney homotransplants, using cutaneous ureterostomy, and that several of their homografts have functioned for several months and are still functioning.

In the experimental laboratory we have used the splenic pedicle as the site of renal autotransplantation, employing cutaneous ureterostomy, with good results.

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ACUTE STAPHYLOCOCCIC ENDOCARDITIS CURED WITH THE AID OF BACITRACIN

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The accompanying case of staphylococcic endocarditis is reported because it is the first instance in which recovery from this disease may be credited largely, if not entirely, to the use of bacitracin. Although the recovery rate from subacute bacterial endocarditis is very high if appropriate antibiotic therapy is instituted within a few weeks after onset, the outlook in cases of acute bacterial endocarditis, including those of staphylococcic endocarditis, is still very poor. Only five of the patients in the 25 cases of Staphylococcus aureus endocarditis collected by Wilhelm and others [1] recovered after penicillin therapy, and only three patients in the nine cases studied by Levinson and others [2] recovered after treatment with penicillin and aureomycin. The cure in the case presented here merits particular attention because the clinical manifestations were extremely severe and control of the infection had not been attained despite two weeks of treatment with massive doses of penicillin, aureomycin, and chloramphenicol.

It is important to call attention to the usefulness of this additional antibiotic, bacitracin, in the control of staphylococcic endocarditis because in some, or many, cases the causative organism may be more sensitive to bacitracin than to penicillin or other available antibiotics. Recent reports indicate that more than 50% of the strains of Staph. aureus isolated are now resistant to penicillin.[3]

Finally, some interesting observations will be noted as to the nature of a urinary abnormality that occurred in the course of parenteral bacitracin therapy.

REPORT OF A CASE

A 28-yr.-old diamond cutter was admitted to Mount Sinai Hospital for the first time on May 30, 1950, with a chief complaint of chills and fever of 10 days' duration. Since his childhood the patient, who had no history of rheumatic fever, had been regarded as a "cardiac," had attended special classes in school,

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2. Levinson, D. C.; Griffith, G. C., and Pearson, H. E.: Increasing Bacterial Resistance to the Antibiotics: A Study of 46 Cases of Streptococcus Endocarditis and 18 Cases of Staphylococcus Endocarditis, Circulation **2**: 668, 1950.

3. (*a*) Barber, M., and Rozwadowska-Dowzenko, M.: Infection by Penicillin-Resistant Staphylococci, Lancet **2**: 641, 1948. (*b*) Hirsh, H. L.; Dowling, H. F., and Robinson, J. A.: Organisms Resistant to Penicillin, Arch. Int. Med. **82**: 310 (Sept.) 1948. (*c*) Nichols, D. R., and Needham, G. M.: Aureomycin in Treatment of Penicillin Resistant Staphylococcus Bacteremia, Proc. Staff Meet., Mayo Clin. **24**: 309, 1949. (*d*) Forbes, G. B.: Infection with Penicillin Resistant Staphylococci in Hospital and General Practice, Brit. M. J. **2**: 569, 1949. (*e*) Bergelman, P. M., and Rantz, L. A.: The Clinical Importance of Coagulase-Positive Penicillin-Resistant Staphylococcus Aureus, New England J. Med. **242**: 353, 1950.

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and had been deferred from military service. For five years he had occasional episodes of palpitation, and two years prior to admission he was digitalized and placed on maintenance doses of this drug.

Two weeks prior to admission the patient became listless and three days later experienced chills and fever with the temperature rising as high as 106.8 F. At the onset of his illness he was treated with penicillin for three days with no apparent effect; he was therefore admitted to a hospital where three cultures of blood and agglutination tests for Salmonella and Brucella organisms were taken and reported negative. A diagnosis of subacute bacterial endocarditis seemed probable despite the negative cultures. He was treated with 4 gm. of aureomycin daily with an unsatisfactory response. Therapy was therefore changed to the daily administration of 5 million units of procaine penicillin combined with 2 gm. of streptomycin parenterally and 4 gm. of chloramphenicol for five additional days. Despite this combined antibiotic therapy, the patient continued to have a high spiking temperature. Petechiae were observed in the eye grounds, and tender spots appeared in the fingers and toes. The patient experienced a sharp attack of pain in the left upper quadrant of the abdomen after the 12 days of therapy described above.

Examination Findings.—On admission to Mount Sinai Hospital the patient was obviously acutely ill. The temperature ranged daily between 100 F. and 106 F. The blood pressure was 132/74. The heart was enlarged almost to the anterior axillary line with the point of maximum impulse in the sixth interspace just within the anterior axillary line. The rhythm was grossly irregular due to auricular fibrillation. There was a grade III apical systolic murmur, harsh, loud, and well transmitted to the axilla. A soft apical diastolic rumble was also audible at the apex. The liver was enlarged 4 cm. below the right costal margin, smooth, and nontender. The spleen was palpable. There was minimal clubbing of the fingers, and on the left thumb there was a small, nontender, erythematous patch 3 mm. in diameter. Scattered, tiny, reddish macules were noted on the small toe of the right foot. There was no abnormality in the lungs.

Laboratory Data.—The urine was alkaline; its specific gravity was 1.026. There was a trace of albumin. The sediment revealed six to eight white cells, four to six red cells, and many granular casts. The hemoglobin content was 11.9 gm. The red blood cell count was 3,950,000. The white blood cell count was 20,200, of which 59% were segmented neutrophils, 36% band forms, 2% lymphocytes, and 3% monocytes. The electrocardiogram showed auricular fibrillation, left axis deviation, and a low T wave in lead 1. The blood urea nitrogen was 18 mg., the fasting blood sugar 80 mg., the serum bilirubin 0.4 mg., and the serum cholesterol 131 mg. per 100 cc. The erythrocyte sedimentation rate was 26 mm. per hour (Westergren). The cephalin flocculation reaction was 2 +. The sternal marrow was very cellular and showed no significant abnormality.

Course.—Within eight hours after admission the patient had a shaking chill, and his temperature mounted to 106.8 F. A culture of blood drawn at this point yielded 26 colonies of Staph. aureus A a cubic centimeter. It was now apparent from the clinical course and the causative organism that the patient was suffering from acute, not subacute, bacterial endocarditis. Since the portal of entry of the causative organism is usually more apparent in acute bacterial endocarditis than in the subacute form and since the Staphylococcus is often introduced through an infection of the skin, the patient was reexamined with these facts in mind. Tenderness and swelling were found to be present over the medial aspect of the right great toe. Review of the history disclosed that there had been a purulent infection at this site and that it had been grossly manipulated immediately preceding the onset of the present illness. On May 31, the day after admission, the patient received 4 million units of crystalline penicillin, and on June 1 the dose was increased to 3 million units every three hours (24 million units daily) and 1 gm. of aureomycin every four hours. After three days of this regimen the temperature still rose to 104 F. The clinical appearance improved slightly at first but then grew rapidly worse. On June 3, the fourth hospital day, a positive blood culture of Staphylococcus was again obtained, but only in one flask. Because two weeks had now elapsed since the onset of the disease without control of the infection, despite the use of penicillin in huge doses alone and in combination with aureomycin and chloramphenicol in full dosage, and because of the well-known speed at which acute bacterial endocarditis runs a fatal course, more vigorous antibiotic therapy or a modification in treatment appeared urgently indicated.

A review of the sensitivity of the causative Staphylococcus (table 1) revealed that it was moderately resistant to penicillin in vitro, but the dosage administered was theoretically more than adequate to control the infection. The microorganism was even more sensitive to aureomycin and chloramphenicol in vitro, but clinically aureomycin and chloramphenicol had proved ineffective. The most potent antibiotic in vitro was bacitracin, which inhibited growth with half the concentration needed to inhibit the standard test organism. Furthermore, the causative Staphylococcus was extremely sensitive to a combination of bacitracin

TABLE 1.—*Sensitivity of the Infecting Organism, Staph. Aureus*

Antibiotic	Concentration, per Cc.	Index of Resistance (X Standard)
Penicillin	0.3 units	15.0
Aureomycin	0.4 γ	2.0
Terramycin	0.6 γ	3.0
Chloramphenicol	2.0 γ	3.3
Bacitracin	0.2 units	0.5
Penicillin	0.09 units	in combination
Bacitracin	0.06 units	
Penicillin	0.12 units	in combination
Aureomycin	0.16 γ	

and penicillin, much more so than to bacitracin or penicillin alone or to the combination of penicillin and aureomycin.

Accordingly, bacitracin therapy was begun the evening of June 4, the fifth hospital day, with 10,000 units administered intramuscularly every four hours. The bacitracin in combination with the penicillin and aureomycin produced a blood level of more than 40 units of penicillin activity and a bacitracin level of 17 units per cubic centimeter of serum (table 2). There followed a progressive decline in temperature; within two days the temperature did not exceed 101 F. and thereafter fell over a week's time to levels between 99 F. and 100 F. With the abatement of fever there was a concomitant improvement in the remainder of the clinical course. Except for one brief episode of tenderness of the left costovertebral angle on June 10, the embolic phenomena subsided.

TABLE 2.—*Antibacterial Activity of Serum After Antibiotic Administration*

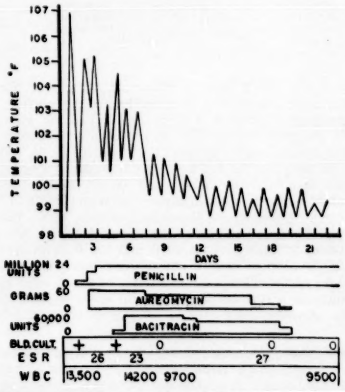
Date	Antibiotic	Dosage, Units	Antibiotic Level of Serum 3 Hours After Administration (Staph. Aureus A Units per Cc.)
6/2/50	Penicillin Aureomycin	3 million q 3 h 1.0 Gm. q 4 h	Total 8
6/7/50	Penicillin Aureomycin Bacitracin	3 million q 3 h 1.0 Gm. q 4 h 10,000 q 4 h	Total greater than 40 Bacitracin level 17 (bacitracin units per cc.)
6/21/50	Penicillin	3 million q 3 h	20
6/26/50	Penicillin	3 million q 3 h	13
7/3/50	Penicillin	3 million q 3 h	13
7/11/50	Penicillin	3 million q 3 h	10

The patient tolerated the large doses of aureomycin poorly, suffering intense nausea and vomiting even before bacitracin was given. The oral administration of aureomycin was therefore discontinued on June 14, and 900 mg. of aureomycin a day was administered intravenously for two days and omitted thereafter.

The bacitracin dosage was reduced to 40,000 units daily on June 9, the seventh day of its use, and after an additional seven and one-half days it was discontinued. A culture of blood drawn on June 17 showed no growth. Penicillin was continued, the dosage being 24 million units a day, until June 19.

The urinary findings were of particular interest. The urine was studied daily and was consistently acid, with a specific gravity of 1.026 on admission and with random specimens consistently above 1.022, during the entire course of bacitracin therapy. Subsequently, slightly lower values were found, but before the patient's discharge values of 1.024 were again noted. Albu-

minuria was present only in faint traces. There was no significant abnormality in the sediment. Reducing tests for sugar were negative until June 17, the 14th day of bacitracin therapy, when a positive reaction equivalent to 1 + to a test for glucose was obtained. Thereafter the urine was tested at frequent intervals revealing the same positive reaction. At no time was acetonuria noted. The fasting blood sugar was 80 mg. per 100 cc., and an oral glucose-tolerance test revealed a normal curve. The blood urea nitrogen remained normal, and urine culture showed only Staphylococcus albus B. The reducing substance in the urine was studied, and it was demonstrated that while the color of a copper solution was changed no copper oxide precipitated at room temperature. There was no fermentation with yeast, and tests for pentose were negative. The reducing substance disappeared on July 19. One month later tests for this reducing substance failed to reveal its presence. Previous workers [4] noted excretion of approximately 25% of the administered dose of bacitracin in the urine, with urinary concentrations not exceeding 50 units a cubic centimeter. Because the bacitracin itself may have been responsible for the reducing reaction, tests for reducing properties were made with 200 units a cubic centimeter of bacitracin, as well as with lower concentrations. In no instance was there a positive reducing reaction.



Clinical course first 22 days at Mount Sinai Hospital. First hospital day represents 13th day of illness. Prior to this hospitalization large doses of penicillin, streptomycin, aureomycin, and chloramphenicol had been administered without effect.

The patient was discharged on July 24, 1950, after 56 days of hospitalization. He was afebrile. His heart murmurs were unchanged, and the spleen was no longer palpable. The blood leukocyte and differential count were normal. A mild anemia and an elevation of sedimentation rate were present. The urine was normal except for a trace of albumin. The blood urea nitrogen was normal. Three daily consecutive cultures of blood taken after all antibiotic therapy was discontinued revealed no growth. During his stay at Mount Sinai Hospital the patient had received a total of 660,000 units of bacitracin in 15 days, 1 billion 11 million units of penicillin in 44 days, and 66 gm. orally and 2.1 gm. intravenously of aureomycin in 17 days. He has remained well up to the time of writing, five months after treatment was completed.

COMMENT

The clinical differentiation between acute staphylococcic bacteremia without endocarditis and acute staphylococcic endocarditis is often difficult. The chills and extremely high fever, the positive blood culture, and even the splenomegaly occur in either disease. In this case the additional findings of rheumatic cardiovalvular disease, petechiae, an Osler node, and the absence of an active bacterial focus (other than valvular vegetations) which could maintain the bacteremia supported the diagnosis of acute bacterial endocarditis. Since there was no striking change in the character of the murmur and no development of a new murmur, there is no direct evidence that bacterial vegetations actually involved the endocardium. However, the diagnosis of bacterial endocarditis appears justified whenever a persistent bacteremia is found in the presence of a valvular lesion and in the absence of any other overt bacterial infection in direct contact with the blood stream.

The knowledge that acute bacterial endocarditis usually runs its complete and fatal course within four weeks interdicted any prolonged periods of experimental therapy and impelled us to rapid modifications when a brief trial of a given regimen failed to give prompt evidence of control of the infection. Furthermore, delay in appropriate therapy might court the risk of suppurative focuses in the brain or other organs that would be difficult to eradicate with doses of antibiotics which would have been effective earlier. Since the temperature, after a slight fall, had risen to 104 F. and the patient's clinical condition had not significantly improved, despite a week's treatment with at least 5 million units daily of penicillin and three days of treatment with 24 million units daily of penicillin together with the 4 to 6 gm. daily of aureomycin and chloramphenicol given previously, further change in therapy was considered urgently indicated. At this point bacitracin therapy was instituted, both because the other antibiotics had failed and because in vitro sensitivity studies indicated that bacitracin might be more effective. For the reasons mentioned above and because bacitracin alone had not yet been found curative in cases of staphylococcic endocarditis, the penicillin and aureomycin were continued together with the bacitracin. The in vitro studies had also indicated that penicillin and bacitracin in combination were much more effective against the causative Staphylococcus in this case than bacitracin alone.

Because the other antibiotics were continued, it is difficult to assess accurately the relative importance of bacitracin in effecting recovery. It was felt that the patient's condition was critical and had been deteriorating under penicillin and aureomycin therapy and that there was a striking and rapidly favorable clinical response to the addition of bacitracin therapy. Credit for recovery may be given to the action of bacitracin on the basis of other objective data, namely, the persistent fever and positive blood culture on the day that bacitracin therapy was begun and the rapid lysis of fever and the negative blood cultures after the therapy was instituted. Nevertheless, the possibility cannot be excluded that the penicillin alone or in combination with aureomycin might have eventually effected a cure since the temperature had been reaching lower levels (104 F.) and the blood culture, although still positive, suggested that relatively fewer organisms were present in a unit of blood. It is also uncertain whether the bac-

4. Zintel, H. A.; Ma, R. A.; Nichols, A. C., and Ellis, H.: The Absorption, Distribution, Excretion, and Toxicity of Bacitracin in Man, Am. J. M. Sc. **218**: 439, 1949.

itracin alone would have been equally effective or whether the potentiating effect of combined penicillin and bacitracin was essential.

With respect to staphylococcic infections in general and staphylococcic endocarditis in particular, the availability of bacitracin as an effective antibiotic is especially timely. An increasing number of reports [3] indicate that more and more strains of staphylococci are becoming resistant to penicillin, hitherto the preferred antibiotic against staphylococci. British workers [3a,d] have reported that as many as 60 to 70% of the strains of staphylococci isolated from hospital patients were resistant to penicillin. Reports in this country also indicate that there has been a striking and sudden increase in the percentage of penicillin-resistant strains of staphylococci.[3c,e] Penicillin resistance is apt to be of particularly serious consequence in cases of bacteremia or endocarditis. Nichols and Needham [3c] reported from Mayo Clinic that in a series of 15 patients with bacteremia due to Staph. aureus the organism was resistant to penicillin in 12 instances. Similarly, Hirsh and associates [3b] isolated penicillin-resistant staphylococci in four cases of bacteremia or endocarditis. The importance of establishing the efficacy of other antibiotics against these penicillin-resistant staphylococci is apparent. Streptomycin may be effective in vitro, but resistance to this antibiotic develops during therapy.[3c] Aureomycin has sometimes proved effective in generalized staphylococcal infections after penicillin has failed [5] but did not control the infection in our case or in a case described by Astler and Morgan.[6] The development of resistance to aureomycin in cases of staphylococcic endocarditis was noted by Levinson and associates.[2] The encouraging experience with bacitracin suggests that this antibiotic may supply a much needed additional effective agent against these serious staphylococcic bacteremias with and without endocarditis.

There have been several reports on the nephrotoxic activity of bacitracin.[7] By means of clearance techniques reduction in both glomerular and tubular function was demonstrated.[7e] Proteinuria was a constant early finding but disappeared rapidly (in 16 days); whereas, the reduced glomerular and tubular function required seven to nine weeks for recovery.[7e] It is uncertain whether the toxicity is due to impurities or to bacitracin itself. The observation that toxicity was much more frequent in lots of bacitracin prepared by the deep tank method than by the surface method suggests that the toxicity may be due to impurities. The gravity of the case presented here appeared to warrant the use of bacitracin despite reports of its nephrotoxicity. No significant increase in proteinuria occurred, and, while the specific gravity of random specimens fell slightly, there was no significant reduction in concentrating power of the kidney. Several authors have observed that "fasting glycosuria" has occurred under bacitracin therapy.[7d,e] Positive reactions to reducing tests for glucose were obtained here also, but it was demonstrated that the reducing substance was neither glucose nor pentose. The findings in this case indicate that while a reducing substance may appear in the urine of bacitracin-treated patients there is no glycosuria. The nature of the reducing substance was not identified. Bacitracin itself is not a reducing substance in concentrations up to 200 units a cubic centimeter.

No significant toxic manifestations of a gastrointestinal nature or local reactions at the site of injection were noted.

5. Dowling, H. F.; Lepper, M. H.; Caldwell, E. R., Jr.; Whelton, R. L., and Sweet, L. K.: Aureomycin in Various Infections: Report of 180 Cases and Review of the Clinical Literature, M. Ann. District of Columbia **18**: 335, 1949. Nichols and Needham.[3c]

6. Astler, V. B., and Morgan, H. R.: Some Biologic Complications of the Prophylactic and Therapeutic Use of Antibiotics, Univ. Hosp. Bull., Ann Arbor **16**: 127, 1950.

7. (*a*) Meleney, F. L., and Johnson, B. A.: Bacitracin, Am. J. Med. **7**: 794, 1949. (*b*) Michie, A. J.; Zintel, N. A.; Ma, R. A.; Ravdin, I. S., and Rapni, K.: The Nephrotoxicity of Bacitracin in Man, Surgery **26**: 626, 1949. (*c*) Smith, L. W.; Schultz, F. N., Jr.; Ott, W. L., and Payne, H. G.: A Comprehensive Study of the Renal Damage Produced in Mice by Various Lots of Bacitracin, J. Clin. Investigation **28**: 1018, 1949. (*d*) Scudi, J. V.; Corit, A., and Antopol, W.: Some Pharmacological Properties of Bacitracin: III. Chronic Toxicity of Commercial Bacitracin in the Dog and Monkey, Proc. Soc. Exper. Biol. & Med. **66**: 558, 1947. (*e*) Miller, J. H.; McDonald, R. K., and Shock, N. W.: The Effect of Bacitracin on Renal Function, J. Clin. Investigation **29**: 389, 1950. (*f*) Zintel, Ma, Nichols, and Ellis.[4]

SUMMARY

This is a report of the first case of acute Staph. aureus endocarditis in which cure followed the parenteral use of bacitracin in conjunction with other antibiotics. The bacitracin appeared to be effective after the disease had not been controlled by huge doses, over a period of 12 days, of penicillin, aureomycin, and chloramphenicol. No significant renal or other toxicity was associated with the administration of bacitracin. A reducing substance, previously regarded as glucose, was also noted in this case during bacitracin therapy. It was, however, demonstrated to be neither glucose nor pentose. Because of the increasing frequency of penicillin-resistant strains of Staph. aureus, the availability of bacitracin as another potent antibiotic in serious staphylococcic bacteremias and endocarditis is noteworthy.

Dr. Frank L. Meleney supplied the bacitracin used in this case.

1088 Park Ave. (Dr. Friedberg).

Schism in Psychiatry.—The psychiatric view of man has changed in half a century. Fifty years ago, the psychiatrist was likely to see only the somatic man. . . . The general psychiatric quest was for central nervous system pathology to explain the various derangements. . . . The reaction which followed, placed emphasis on psyche rather than soma, on function rather than structure. Here, however, even when there was great protestation that the psyche was a function of a somatopsychic entity, that all psychiatric disorders must be considered in relation to physical factors, constitution, or biological determinants, there was a tendency to discuss mental disorders as if the soma did not exist. Meyer was one of the few to raise a voice against this professional schizoid behavior; and Meyer was venerated rather than followed; while Freud, his pupils and the deviant psychoanalytic schools, who all emphasized verbally that they were convinced of important somatic factors, did little to establish or study them.

It is questionable if shock treatment and the psychosurgical procedures have dipped the balance back toward a somatic orientation. . . . Psychosomatic medicine has thrown a bridge across the psychiatric gap, but it has been too narrow to accommodate the full breadth of the concepts on either side. It has given access to a new field, rather than helped in exploration of the fundamental relationships of psychic and somatic factors in the major psychiatric disorders. Any full exploration will include, among many things, hormone relationships.—"Brighten the Corner," an editorial in the *Psychiatric Quarterly*, April, 1951.

COUNCIL ON NATIONAL EMERGENCY MEDICAL SERVICE

This paper is one of a series requested by the Council on National Emergency Medical Service to inform the medical profession on problems pertaining to civil defense. It does not necessarily reflect, however, the opinions of the Council or of any other official body unless so stated in the article.

C. JOSEPH STETLER, *Secretary.*

ATOMIC BOMB INJURY: RADIATION

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The syndrome of acute radiation injury to be considered in this article is the term applied to the symptom complex, or diseased state, which results from exposure of the whole body or a major portion of it to the initial nuclear radiation of an atomic bomb. This term should be clearly distinguished from irradiation sickness, which is commonly used to describe the symptom complex resulting from therapeutic irradiation. It should also be distinguished from surface radiation injury. This term is properly applied to injuries of the skin and subcutaneous tissues resulting from x-radiation or from contact or near contact with radioactive material, such as fission products and induced radioactivity. Injuries of this type related to atomic energy are due largely to beta-ray-emitting isotopes. Internal radiation injury may result from the selective deposition, such as in bone or thyroid, of radioactive material that has been inhaled or absorbed through the gastrointestinal tract or wounds. The two latter types of radiation injury may be caused by residual radioactive contamination.

Initial nuclear radiation from an atomic bomb consists of gamma rays and neutrons emitted during the first minute after atomic explosion. Approximately one-half of the initial nuclear radiation is delivered in the first second, and 98% has been delivered by the end of one minute. The syndrome of radiation injury due to exposure of the whole body may occur as a result of any sort of atomic explosion: air burst, surface burst, or underwater burst. In an air burst or a surface burst, persons who are in the open, unshielded by buildings or natural objects, will constitute the most exposed group for any given distance. Those who are shielded by natural objects or who are in buildings made of brick, concrete, or metal will be less exposed, and those who are in tunnels, caves, or air raid shelters will be the least exposed.

When the data of the Japanese casualties were analyzed, it was found that it was possible to evaluate, in a general way, the effect of shielding afforded by buildings and shelters. The symptoms and the results of radiation injury to persons who were inside buildings were equivalent to those observed in persons who were in the open, unshielded, and approximately 500 yards farther away from the bomb. It is evident from animal experiments that effective shielding of some portion of the body, such as the spleen, the head, or the abdomen, may reduce the mortality. Only those who were certainly in the open and unshielded, or were in wooden buildings, can be assumed to have received the maximum dose of initial nuclear radiation which could be expected at a given distance. It is proper to assume that all others have received less than the dose that is theoretically possible. It is apparent that it will not be desirable to classify casualties solely on the basis of their distance from the bomb burst.

CLINICAL CLASSIFICATION OF THE SYNDROME OF ACUTE RADIATION INJURY

On the basis of the study of the Japanese casualties, and by analogy with other forms of trauma, casualties may be divided roughly into two classes: (1) uncomplicated radiation injury and (2) radiation injury complicated by burns and wounds. It is not now known how important such complications may be, but it appears that the effect may be considerable. This paper will be limited to uncomplicated radiation injury.

The syndrome of acute radiation injury due to exposure of the whole body to the initial nuclear radiation of an atomic bomb was found to occur in three fairly distinct forms, the features of which are summarized in the following outline:

1. Very severe cases (in general, radiation exposure of 600 r or more).
   - (*a*) First day.
     Malaise, nausea and vomiting beginning one to two hours after exposure and continuing for several days.
     Prostration.
     Rapidly developing and persistent severe leukopenia.
   - (*b*) Next few days.
     Diarrhea and rising sustained fever.
   - (*c*) Up to two weeks.
     Death in coma and delirium within 14 days after exposure.
     Purpura and epilation may appear shortly before death.

2. Severe cases (in general, radiation exposure of about 400 r).
   - (*a*) First day.
     Nausea and vomiting usually occurring a few hours after exposure but rarely persisting more than 24 hours.
   - (*b*) Second day.
     Lymphopenia (about 800 lymphocytes per cubic millimeter).
     Total leukocyte count variable.
   - (*c*) Fourth to 20th days.
     First, a period of relative freedom from symptoms, with:
     (1) Perhaps some malaise and easy fatigability.
     (2) Persistent lymphopenia.
     (3) Fluctuating leukopenia.

The opinions and assertions contained herein are the personal ones of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy, the Naval Service at large, or the Atomic Energy Commission.

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Then, at any time up to the 20th day, the individual may become seriously ill, showing any or all of the following symptoms:
(1) Epilation (chiefly limited to scalp).
(2) Purpura and other hemorrhagic complications such as melena, epistaxis, menorrhagia, and metrorrhagia.
(3) Oropharyngeal ulcerations.
(4) Diarrhea.
(5) Fever.
(6) Severe leukopenia.
(7) Infection and breakdown of healing wounds.
(8) General sepsis.

(*d*) 20th to 40th days.
Death occurs in 50% of untreated persons with sepsis or with hemorrhagic manifestations dominating the picture.

3. Mild to moderately severe cases (in general, radiation exposure of 200 to 300 r).
(*a*) First day.
Vomiting may occur a few hours after exposure.
(*b*) Next two weeks.
No definite symptoms.
Moderate lymphopenia.
(*c*) After two weeks.
One or a few of the following may appear:
(1) Epilation (chiefly limited to scalp).
(2) Malaise.
(3) Sore throat.
(4) Petechiae.
(5) Diarrhea.
(6) Weight loss.

Very Severe Radiation Injury.—In this form, vomiting commences shortly after the bombing and may persist for several days. Progressive malaise leading to prostration begins shortly after the bombing, and symptoms continue unabated until death. Diarrhea usually appears within a few days and persists. Fever of the sustained type occurs within a few days of the bombing and increases progressively. Without therapy, death is invariable and may occur at any time from a few hours up to 14 days. Epilation and purpura may appear shortly before death. Hemorrhagic manifestations do not seem to be responsible for the fatal outcome. Progressive leukopenia is present from the day of the bombing.

Severe Radiation Injury.—In this form, vomiting occurs shortly after the bombing and seldom lasts longer than the first day. A latent period follows, during which the only symptom is increasing malaise. The end of the latent period occurs in four to 20 days and is marked by the appearance of one or all of the following characteristic symptoms of radiation injury: epilation, purpura, other manifestations of the hemorrhagic state, and oropharyngeal lesions. Concurrently, a variety of conditions may develop (diarrhea, infection and breakdown of healing wounds). The patient rapidly becomes very ill with fever, and prostration and a severe hemorrhagic state may occur. If death follows, it is usually due to acute blood loss, septicemia, or hemorrhage into vital structures. Death may occur at any time between the third and sixth week after the bombing. The hematological findings in these patients are most pronounced during the third to the fifth week and consist of severe leukopenia, thrombopenia, anemia, and prolonged bleeding and clotting time. As recovery occurs, the hemorrhagic manifestations subside and spontaneous defervescence takes place. Among the Japanese, the mortality rate for patients with severe radiation injury varied from 25% to more than 50%. It is convenient to consider that severe radiation injury in man is equivalent to the type of injury that occurs in experimental mammals given a comparable dose of x-rays.

Mild to Moderately Severe Radiation Injury.—In this form, any of the characteristic symptoms may occur, but it is distinctly unusual for all of them to be present. The interval between exposure and the occurrence of the general symptoms is longer than in the preceding types. The changes in the hemogram are less profound than in the severe forms, and they occur somewhat later in the course of the disease. Recovery is the rule for better than 90% of patients with moderately severe radiation injury. The deaths that occur are usually the result of complications, such as tuberculosis, bronchiectasis, chronic abscesses, and refractory anemia, and as a rule occur later than the sixth week.

Since the number of persons exposed to an atomic bomb increases geometrically with the distance from the explosion, it follows that there will be more patients with the mild to moderately severe type of radiation injury than with the severe type. The smallest group would ordinarily be the very severe cases. Because of the large number of casualties produced by a single atomic explosion, it is of the utmost importance to estimate, as promptly as possible, the severity of the radiation injury experienced by each patient. It is obviously uneconomical of medical supplies and medical personnel—and, in fact, unnecessary—to devote much attention to patients with moderately severe and mild radiation injury.

In general, few who are farther than one mile from the site of an atomic bomb [1] explosion will experience the syndrome of severe radiation injury, regardless of whether they were shielded or outdoors. Badly burned patients may be an exception to this rule, but they would require extensive medical care for their burns in any event. On the basis of our present knowledge, it would appear that the syndrome of severe radiation injury, uncomplicated by burns or wounds, would develop in not more than 5% of those who received less than 200 r. Regardless of whether the exact location of the person at the time of exposure is known, or whether personnel dosimeters are available, the severity of the radiation injury can be judged with fair accuracy, once the symptoms have developed, by an evaluation of the symptoms and the laboratory findings.

CLINICAL DIAGNOSIS OF RADIATION INJURY

Analysis of the data collected by the Joint Commission for the Investigation of the Effects of the Atomic Bomb in Japan disclosed that in persons exposed to an atomic explosion, epilation and purpura could be designated specific symptoms of radiation injury. Three other symptoms were designated suggestive symptoms of radiation injury: vomiting on the day of the bombing, oropharyngeal lesions which occurred before the 39th day, and hemorrhagic manifestations other than cutaneous purpura. A variety of other symptoms were

1. The type of atomic bomb referred to is equivalent to 20 kilotons of trinitrotoluene (TNT).

subjected to statistical evaluation, such as anorexia, malaise, diarrhea, bloody diarrhea, and fever, but the degree of correlation was low.

Among the Japanese, epilation commenced during the second week after the bombing and was largely confined to the hair of the scalp. The mean day of onset of epilation was the 25th. Regrowth of hair was apparent after the sixth week in most surviving patients and was usually complete by the fourth or fifth month.

Among the Japanese, purpura was of the cutaneous variety, such as would be readily apparent on inspection. It was rarely observed before the third week, and the mean day of onset was the 24th. In general, patients with cutaneous purpura which was extensive displayed other signs of the hemorrhagic state.

These two symptoms, epilation and purpura, offer the best clinical indication of the severity of the exposure to radiation. Patients with both these symptoms usually had the suggestive symptoms referred to above. It was found that patients with both these symptoms had the lowest leukocyte counts.

As presumptive evidence of radiation injury, vomiting on the day of the bombing is most significant. Its early occurrence, and the fact that it is not likely to be overlooked by the patient, makes it of great help in triage and in evaluation. It is of interest that the Japanese physicians attributed the vomiting on the day of the bombing to psychological causes. However, when the large volume of clinical data was subjected to analysis, the relation between this symptom and probable exposure was indubitable.

The oropharyngeal manifestations consisted of a dusky inflammation of the mucous membrane, soreness of the gums, and, in severe cases, an ulceronecrotic breakdown of the tissues; such changes were rare before the third week, and the mean day of onset was the 22nd. In severe cases, the appearance of the lesions resembled those seen in agranulocytic angina. In some patients, the laryngeal and the upper tracheal mucosa were affected similarly.

The hemorrhagic manifestations other than cutaneous purpura included epistaxis, menorrhagia and metrorrhagia, melena, hemoptysis, hematuria, and bloody emesis. Most patients with cutaneous purpura of any extent also had some or all of these hemorrhagic manifestations. In some whose exposure to radiation was less than the amount required to cause severe radiation injury, these other hemorrhagic manifestations occurred in the absence of cutaneous purpura. This suggested that in certain persons with pre-existing disease, a mild hemorrhagic state tended to produce gross hemorrhage in the diseased tissue (e. g., with pulmonary tuberculosis or uterine fibroids).

The most serious obstacle to the clinical determination of the severity of radiation injury is the late appearance of the clinical symptoms. In general, the earlier the appearance of the so-called specific or suggestive symptoms, the severer the radiation injury.

LABORATORY DIAGNOSIS OF RADIATION INJURY

There is no single laboratory procedure that is by itself diagnostic for radiation injury. Severe radiation injury to the whole body produces pronounced leukopenia (lymphopenia and granulopenia), thrombopenia, and anemia.

Total Leukocyte Count.—Leukopenia invariably follows whole body radiation injury. In the very severe type the leukocyte count falls to less than 1,000 per cubic millimeter within the first week. With less severe degrees of radiation injury the lowest white cell counts are seen two to four weeks after exposure. It was the opinion of the Japanese physicians that recovery was unlikely if the total leukocyte count was less than 500 per cubic millimeter.

Lymphocytes.—In the first few days after exposure the lymphocyte count has greater diagnostic value than the total leukocyte count. Lymphocytes start to decrease immediately after exposure. Pronounced lymphopenia appears within 24 hours. A total lymphocyte count less than 800 per cubic millimeter 48 hours after exposure is presumptive evidence of severe radiation injury. A lymphocyte count in excess of 1,500 per cubic millimeter 48 hours after an atomic bombing indicates that radiation injury of clinical significance is unlikely.

Neutrophilic Granulocytes.—With severe radiation injury, the neutrophils decrease less rapidly than the lymphocytes. With doses of radiation that are uniformly fatal to experimental animals the total granulocyte counts are less than 1,000 per cubic millimeter within one week. With lesser doses of radiation, such low levels may be attained but it takes much longer, perhaps 10 to 20 days.

Thrombocytes.—For the first three to four days following severe radiation injury, the thrombocyte count remains fairly stable. Beginning four to five days after exposure, the thrombocyte count drops rapidly, attaining values close to zero during the second week. Thrombocytes may remain at this low level for two to four weeks.

Anemia.—In severe radiation injury, anemia develops slowly. It may be two to three weeks before it is evident. The lowest red cell counts are observed four to five weeks after exposure. A rapidly decreasing blood hemoglobin, red blood cell count, or hematocrit is a serious sign and suggests rapid blood loss.

Reticulocytes.—Reticulocytes decrease in number promptly and are almost absent for three to four weeks. Any subsequent increase in reticulocytes is a good prognostic sign.

A prominent clinical symptom of radiation injury is the hemorrhagic state that begins between the second and fourth week. The severity of this hemorrhagic state is closely correlated with the level of thrombopenia. It is characterized by an increased capillary fragility, prolonged bleeding time, and prolonged clotting time.

SUMMARY OF THE DIAGNOSIS OF RADIATION INJURY

The diagnosis of the syndrome of radiation injury and the estimation of its severity depend on a proper evaluation of three factors: 1. The probability that nuclear radiation sufficient to cause injury reached the patient. This will depend on a knowledge of the patient's location at the time of the bombing, and the estimate of the kilotonnage of the bomb. If personnel dosimeters are available, the data obtained from them

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must be correlated not only with the foregoing but also with the clinical symptoms. 2. The existence or the development of any or all of the typical symptoms of radiation injury. Early after the bombing, it is proper to attach great significance to the presumptive diagnostic sign of vomiting on the day of the bombing. Particular attention should be directed to the tempo at which symptoms develop. Early appearance is indicative of greater severity of radiation injury. 3. The occurrence and the time-trend of leukopenia and lymphopenia are significant, and should aid materially in the accurate evaluation of the severity of the injury. In the absence of cutaneous purpura or other hemorrhagic manifestations, abnormality of clotting and bleeding time does not necessarily imply that the patient has a severe form of radiation injury. In conclusion, the diagnosis of radiation injury and the estimation of its severity constitute, essentially, a clinical problem and should be possible on the basis of a brief history, physical examination, and a minimum of laboratory studies.

TREATMENT OF THE SYNDROME OF ACUTE WHOLE BODY RADIATION INJURY

In the following discussion the recommended therapy is aimed only at the syndrome of radiation injury. Actually, many if not the majority of cases will be complicated by some other type of injury—trauma, burns, or both—which will, of course, require appropriate treatment. Certain general considerations must be borne in mind. At present there are available no specific agents of proved therapeutic value either for prophylaxis or for treatment following radiation. Treatment, therefore, is symptomatic. This does not by any means imply that efforts at therapy are a waste of time.

The syndrome of severe radiation injury (seen in persons who have received in the neighborhood of 400 r) is, essentially, that of a self-limited disease and at the outset resembles agranulocytic angina. As the illness progresses, the hemorrhagic manifestations become more prominent. If the patient can be tided over the two to five week period during which pancytopenia is more or less complete, he will in the majority of instances recover normal bone marrow function and normal ability to combat infection. The purpura and other manifestations of a hemorrhagic state will disappear, the various formed elements will return to their normal concentrations in the blood, and the lymphoid tissue will return in normal abundance. Furthermore, the individual tissues and organs in survivors will show no evidence of radiation damage greater than what they would have sustained singly from the given dose of radiation. Treatment from the very beginning should be directed at minimizing the effects of the tendency to hemorrhage and inability to combat infection. Wounds should be carefully débrided and every effort made to accomplish healing by primary intention in the shortest possible time. This will minimize the tendency for wound disruption during the active stages of the illness. All the symptoms other than the initial nausea and vomiting and the loss of hair seen at Hiroshima and Nagasaki can be adequately explained on the basis of pancytopenia, including thrombopenia, plus disturbances in the normal antibody function against bacterial infection. Certainly there is, at the present time, insufficient evidence to warrant stockpiling of such items as flavonoid compounds, toluidine blue, protamine, and vitamin B_{12}, as essential to the proper treatment of this type of casualty. On the other hand, the data from Japan attest the usefulness of antibiotics and transfusions. The value of antibiotics has been substantiated by a number of experimenters.

In the absence of data to the contrary, efforts to maintain water balance and good nutritional status, whether by oral or parenteral means, would seem to be of the utmost importance in the presence of diarrhea, hemorrhage, and infection.

With these considerations in mind, the treatment of this syndrome can be outlined as follows:

Very Severe Cases.—In general, this includes cases in which upward of 600 r of whole body radiation was received. There is no satisfactory method for treating patients who have received the certainly fatal doses of ionizing radiation which produce this form of the disease. Nausea and vomiting appear in one or two hours, followed by prostration within the first 24 hours. Before attributing such symptoms to severe radiation injury, however, one must rule out other types of injury as well as emotional disturbances that might produce similar symptoms but from which the patient might recover.

Japanese experience indicated that these victims were very sensitive to physical activity, so that they should be given as much rest as possible as soon as possible. They should not be transported long distances. Treatment should emphasize fluid replacement and efforts to restore electrolyte balance and should include sedation when indicated. There would appear to be no particular advantage in the use of antibiotics and blood transfusions in these persons merely on general principles. On the other hand, when there are clear-cut clinical indications for their use, they should be employed.

Severe Cases.—In general, this includes cases in which in the neighborhood of 400 r of whole body radiation was received. These persons need and profit most from good medical treatment. Although in the absence of trauma and burns they do not require active care in the first few days, strenuous activities should probably not be permitted.

Therapy should be directed at (1) restoration of water and electrolyte balance and maintenance of general nutrition, (2) control of infection, and (3) treatment for hemorrhage and anemia. The diet should be bland and low in residue. Intravenous fluids and parenteral alimentation should be given in the usual manner when indicated and when feasible, in an effort to maintain good nutritional status and to restore water and electrolyte balance in the presence of severe gastrointestinal symptoms. Infection can be controlled, at least in part, by the use of antibiotics. There is no reason to begin antibiotic therapy sooner than 48 hours after exposure unless required by wounds, burns, or infectious disease. When there is little doubt that a victim has been exposed to several hundred roentgens, it is wise, if adequate supplies are available, to start oral maintenance doses of an antibiotic by the third or

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fourth day. Once severe symptoms appear, combined oral and parenteral therapy should be instituted. Beginning with several antibiotics at once has not been proved of value. On the other hand, it may be necessary to use various combinations in certain cases.

Sulfonamides are probably not drugs of choice in radiation injury. However, if antibiotics are not available, they would undoubtedly prove lifesaving in certain instances.

The only effective treatment for hemorrhage and anemia is replacement therapy by blood transfusion. It would seem desirable, whenever possible, to maintain blood hemoglobin at a level of 10 gm. or more per 100 cc.

Moderately Severe and Mild Cases.—In general, the treatment is similar to that suggested above, modified, of course, according to the clinical indications.

ULTIMATE PROGNOSIS OF THOSE WHO HAVE SURVIVED SEVERAL HUNDRED ROENTGENS OF WHOLE BODY RADIATION

It is too early to write of the eventual outcome of the Japanese who recovered from radiation injury. Radiation cataracts of varying severity have occurred in an appreciable number of those who were close enough to receive a significant amount of radiation. It appears likely that the incidence of leukemia will be higher among the survivors than in the Japanese population as a whole. There is enough information available now to warrant the statement that the survivors have regained their fertility and that, among the progeny of the survivors at Hiroshima and Nagasaki, no unusual incidence of abnormal offspring has occurred.

COMMITTEE ON MEDICOLEGAL PROBLEMS

The Committee on Medicolegal Problems of the American Medical Association has approved the publication of the following report by Louis J. Regan, M.D., LL.B.

MALPRACTICE AND THE PHYSICIAN

The incidence of malpractice claims increased tenfold during the decade between 1930 and 1940. In some localities, malpractice claims have become so frequent that any patient with a less than perfect end result is a potential malpractice claimant. If this alarming situation were evidence that the medical profession was becoming increasingly inefficient, then the solution would of course be obvious. But the blunt truth is that the majority of all malpractice suits filed are without merit; more than half of them involve physicians who are above the median of their respective groups in skill, experience, and professional standing. The search for a solution to this problem demands an understanding of what actually constitutes malpractice, an analysis of the causes of malpractice claims, and a universal knowledge among physicians as to the positive steps which may be taken to decrease both the relatively few justified claims and the preponderantly greater number of unjustified claims.

ANY PHYSICIAN MAY BE SUED FOR MALPRACTICE

The bringing of a malpractice action does not even suggest that the claim has merit; for any patient may bring such an action against any physician who has attended him professionally. Nevertheless, the practitioner who is the target of the accusation is damaged by the mere filing of the action. Accordingly, it is necessary that every physician understand what constitutes malpractice under the law.

WHAT CONSTITUTES MALPRACTICE UNDER THE LAW?

The law requires that a physician who undertakes to diagnose or to treat a patient must possess the skill and exercise the care commonly possessed and exercised by other reputable physicians in the locality. If he holds himself out as a specialist, he must meet the standards of practice of the specialist in the designated field of practice. These legal interpretations of his duty are not changed if the professional services are rendered gratuitously. It follows, then, that no malpractice charge is justifiable unless the physician's service to the patient does not meet the requirements of good medical practice; unless in the diagnosis or treatment of his patient, the physician omits to do something he should do or does something he should not do in terms of accepted standards of practice. The standard of practice is always determined by what other reputable physicians in the community, or in similar communities, would or would not do in the care of similar cases.

This definition of standards needs further clarification; for medicine is not an exact science, and not all patients who are given medical treatment get well. Many are left with some disability or deformity. There are few conditions in which there is available a sole, specific, universally utilized remedy or procedure. There is frequently a great latitude for honest difference of opinion, and often the attending physician must exercise his best judgment in deciding which of the several methods to adopt. In certain circumstances, the physician's acts or omissions may be so unseemly and shocking as to be generally recognized as reprehensible and supportive of legal liability. On the other hand, complications or untoward and unexpected results are not uncommon, and the mere fact that a patient is not cured or does not progress favorably does not suggest culpable ignorance or negligence on the part of the medical attendant.

UNDER LAW, WHAT SKILL AND CARE HAS THE PATIENT THE RIGHT TO EXPECT?

In the absence of evidence to the contrary, the law presumes that a physician has exercised the ordinary skill and care required of him in treating his patient. He is justified if his conduct of the case would be approved by even a respectable minority of his confreres in the same locality. He may make a mistake in diagnosis or be guilty of an error of judgment; he may use medicines or methods of treatment different from those which some of his colleagues would have used; he may obtain a bad result instead of a satisfactory one; but no one of these things is sufficient to fasten upon him the charge of malpractice. Actionable malpractice consists in doing something that should not be done or in omitting to do something that should be done.

MALPRACTICE SUITS LESSEN PUBLIC'S CONFIDENCE IN MEDICAL PROFESSION

It is of primary importance, of course, that every physician familiarize himself with his legal interpretation of what does and what does not constitute malpractice. But that is only the first part of the control of the malpractice contagion; for experience has taught us that the most meticulous attention to the dictates of good medical practice is not sufficient to ward off unjust claims and that no physician, regardless of his excellence, is immune. The misunderstanding, indeed the ill will, which has been engendered by the great number of unjust malpractice suits has tended to break down the public's confidence in the medical profession. This situation has important and far-reaching implications for both the public and the medical profession; for the public interest is adversely affected when the physician in caring for his patient is forced to give thought, time, and energy to safeguarding himself against the possibility of an unjust malpractice claim. The public should be informed of the facts of this problem, for in the long run, it is the public—in the persons of individual patients—whose well being is being jeopardized. There is no relationship outside the family which is so personal and intimate as that of physician and patient, no relationship in which the character, integrity, and conscience of one party are so important to the well being of the other. The overwhelming majority of

physicians faithfully and unselfishly meet the demands and obligations of their calling; and the majority of patients do not unjustly file malpractice suits. The acts of the ignorant, the greedy, the callous few—among either patients or physicians—must not be permitted to destroy the merited esteem in which the profession as a whole is held.

HOW MUCH SHALL THE PHYSICIAN TELL HIS PATIENT?

As a basic step in improving the situation, the physician must realize that at all times he is obligated to act with the utmost good faith toward his patient. Thus, if he knows that he can not accomplish a cure or that the treatment adopted will probably be of no benefit, he is duty bound to advise his patient of these facts. It is extremely doubtful that a physician has a therapeutic privilege to withhold a specific diagnosis from a patient who is sick with serious or fatal illness. To the contrary, the confidential relationship requires in ordinary circumstances that the physician make a frank and full disclosure of all the pertinent facts to any adult and mentally competent patient. Such completely open handling of a case would do much to improve the physician-patient relationship and to remove the possibility of unjust malpractice actions. However, there are other unavoidable and even psychological factors in the practice of medicine which must also be considered carefully in this respect.

FACTORS THAT PROMOTE MALPRACTICE SUITS

If physicians were always able to obtain perfect results there would be, of course, no malpractice actions. But deaths, untoward and unexpected results, continuing disabilities, and complications occur and will continue to occur. Whether or not the uncured patient brings an action is often determined by his feeling toward the physician. Patients who have a feeling of friendly trust for the physician and who believe that everything possible has been done for them are not so likely to sue for malpractice—even when bad results ensue. Malpractice suits more often arise if the patient is resentful of some fancied or actual affront, if he believes that he has not been sufficiently closely attended, or—above all—if some third person raises a doubt in his mind as to the propriety of the treatment. In regard to this last point, it would be sheer folly to assume that the "third person" is always—or even most often—a layman who is uninformed about the facts of the case. Regrettably, many of these people are physicians who are also uninformed about the details and facts but who precipitate unjustifiable suits by criticising directly or by implication the work of physicians who have cared for particular cases.

Another potential danger to the physician-patient relationship arises from the physician's lack of attention to certain elements of patient psychology as factors in malpractice causation. Although the patient is sick or injured when he comes to his physician, he nevertheless visualizes himself as he was prior to becoming sick—with his body structures intact. Thus, unless the physician understands this viewpoint and prepares the patient properly, the patient with a fracture, for example, is likely to compare the final result with the part prior to injury, not with the injured member as presented to the physician. As another example of patient psychology, the average patient is not disposed to understand an error in diagnosis or the failure to make an early diagnosis. Or again, the unwarned patient is not happy with the surface tissue changes which are sometimes associated with deep x-ray therapy.

An analysis of malpractice claims reveals the significant fact that they arise almost invariably out of the first course of treatment. In other words, it is rare indeed that an old patient instigates a suit against his physician. It is obvious, then, that from the very first contact—indeed, especially with the very first contact—the physician should do everything within his power to develop an honest, frank, and psychologically sound relationship with his patient.

HOW PHYSICIANS MAY SAFEGUARD THEMSELVES AGAINST MALPRACTICE SUITS

The foregoing discussion has analyzed what malpractice is and what can be done in the physician's conduct to avoid real malpractice or to forestall the filing of an unjust claim. But it would be completely unrealistic to assume that any course of conduct on the part of the physician would prevent his being unjustly sued for malpractice. Good medical practice in itself is not enough; the physician must be able to defend his actions by proof of what he has done. He must not only know his legal duty to his patient, but he must fulfil it. He must know and take advantage of every measure to protect himself against the unjustified claim of malpractice. Under present circumstances, it is absolutely foolhardy for any physician to be ignorant of or careless of malpractice prophylaxis. He must take positive actions carefully based upon his legal responsibilities and liabilities.

To begin with, a physician is not legally obligated to undertake the care of any patient. But from the time he assumes the responsibility until he is discharged or withdraws from the case, he must give—or be sure that there is given—the care and treatment required by the condition of the patient. Before a physician may, without legal liability, withdraw from a case he must give reasonable notice of his intention and allow the patient reasonable opportunity to fill his place.

By notice or special contract, the physician may limit the service he is to render. He may agree to treat the patient only at a certain place, or for a limited time, or for certain conditions. On the other hand, he may increase his obligation by expressly agreeing or warranting that he will effect a particular result; in this circumstance, he will be liable on his contract or warranty if he fails to fulfil the agreement. A physician is not an insurer of results unless he makes himself one by his special promise.

Many malpractice actions are brought as the result of some unwise statement made by the attending physician, or his partner, assistant, or office nurse, to the patient or to a friend of the patient. Care should be taken to avoid making any remark constituting an "admission" of fault, or one which may be construed as such. It is understandable that such remarks have been made under emotional stress or when exercising "hindsight" in the face of an unsatisfactory result even when good practice has been followed throughout. A single careless statement might create liability for damages where actually no liability exists. The effect of such a remark when reported to a jury is incalculable and almost impossible to counteract. Further, an admission on the part of the defendant may free the plaintiff from the necessity of offering medical expert testimony.

EXPERT TESTIMONY AND RES IPSA LOQUITUR

Generally, the proof of a physician's negligence must be established by the testimony of medical expert witnesses. The application of the doctrine of *res ipsa loquitur* [1] in a case gives rise to an inference of negligence on the part of the defendant, and relieves the plaintiff of the necessity of proving the alleged malpractice by the testimony of experts. It places on the defendant the burden of making explanation, if he can, to offset the inference of negligence; and by the majority rule a question is created for the jury, regardless of any and all evidence presented by the defendant.

The doctrine of *res ipsa loquitur* has been held applicable in the field of malpractice chiefly in cases which involve (1) slipping instruments, (2) sponges left in the tissues, (3) burns from heating modalities, (4) roentgen radiation injuries, generally limited to cases wherein the roentgen ray is being used diagnostically, (5) infection through the use of an unsterilized needle or instrument, and (6) injury to a portion of an anesthetized patient's body outside the field of treatment or operation.

A GOOD CASE RECORD IS A VALUABLE SAFEGUARD

The importance of good medical case records, as a factor in malpractice prophylaxis can not be overestimated. A good medical case record should contain a history [2] of the case and a physical examination of the patient, together with reports of all indicated laboratory studies. These data constitute the foundation of the medical record and will generally serve as the basis for at least a working diagnosis. If diagnosis is not possible, consulta-

1. *Res ipsa loquitur* (literally, the thing speaks for itself) is a doctrine of the general law of negligence. It is held applicable whenever one person is injured by an instrumentality entirely in the control of another person, the use of which does not ordinarily result in injury if the person in control exercises due care.

2. It is important to indicate the source of the medical history (from the patient, member of family, etc.).

tion is desirable. Consultation reports must be in writing. Thereafter, a good record will reflect (by means of progress notes) a sequential history of the case, its course, complications, and sequelae and, thus, the justification for further or changed investigation and treatment. Such a record will contain a statement of all treatment rendered in the case. Copies of special forms and of reports used or made in a particular case are also a part of a good record. It is desirable that an attending physician ask himself from time to time what he would wish to have in the record of the case under treatment in the event he should later be called upon to justify in court his conduct of the case. If a patient discontinues treatment before he should or fails to follow instructions, the record should show it. A good method is to file a carbon copy of the letter sent to the patient advising him against the unwise course.[3]

UNWARRANTED PROFESSIONAL CRITICISMS PROMOTE MALPRACTICE SUITS

The precipitating cause of a majority of all malpractice actions is found in the unwise comments or criticism of physicians with regard to treatment given to patients by other physicians. Commonly it is criticism by a succeeding physician of the work of his predecessor. Various authorities have estimated that 50 to 80 per cent of all the suits for malpractice would be eliminated if such destructive criticism could be stopped. It is profitless to attempt to determine why physicians are so prone to criticise destructively and unethically, but the results of it are deplorable. Legitimate criticism rests only on full knowledge of the facts as gathered from all parties; from the physician who treated the patient, as well as from the patient.

OTHER PREVENTIVE PRECAUTIONS

The importance of tact can hardly be overemphasized. It should be manifest especially in the handling of the patient and the patient's family; in the avoidance of fee disputes and unwise efforts and methods in the collection of fees (considering the provisions of the statute of limitations); in the avoidance of overoptimistic prognoses and especially of any promise constituting a guarantee of a particular result; in the avoidance of betrayal of privileged communications; in the avoidance of making any statement constituting (or which might be construed as) an "admission" of fault or negligence; in the avoidance of any reference to malpractice insurance protection; and in the securing of legal advice before making any statement in regard to a malpractice claim or suit.

LIABILITY FOR ACTS OF OTHERS

In addition to being responsible for his own acts and omissions, a physician encounters, in his everyday practice, instances in which he may also be responsible for the negligent acts and omissions of others. Thus, he is responsible for the acts of his assistants and employees, for their negligence occurring during the course of their employment. Where doctors practice as partners, each partner is liable not only for his own acts and those of his partner, but for the negligent acts of any agent or employee of the partnership.

When two independent practitioners are caring for a patient, each is liable not only for his own acts but for doing nothing about the negligent acts of the other which he has observed or which in the exercise of ordinary diligence he should have observed.

The attending physician is generally not liable for the negligence of an interne, a nurse, or other hospital employee. He is, however, responsible for the acts of the hospital personnel in so far as they are carried out under his immediate supervision and control. Thus, the operating surgeon and not the hospital is held liable for any negligence of operating room attendants during the performance of surgery.

CONSENT FOR OPERATIONS, TREATMENT AND AUTOPSIES

Consent for operation must always be secured. Any adult in a clear state of mind may authorize operation upon himself. Oral consent might be considered sufficient; but because of the difficulty in proving that it was given, the physician should invariably require a witnessed consent in writing. If the patient is a minor (that is, a person under the age of twenty-one) consent is to be obtained from parent or guardian.[4] If the individual is mentally incompetent, the consent of the one who stands in the position of guardian is required.

When an operation is made compulsory by law (such as vaccination or sterilization [5]) the law furnishes the consent. If an operation is unlawful, consent to the performance thereof does not absolve the surgeon from liability.

In an emergency which demands immediate action for the preservation of the life or health of a patient and in which it is not practicable to obtain his consent or the consent of any one authorized to speak for him, it is the duty of the attending physician to perform without consent such operation as good surgical practice demands.[6]

If sterility is likely to result from the surgery which is contemplated, explanation of that probability should be made and a signed authorization obtained from both spouses. It should be borne in mind that it is hazardous to sterilize any person except upon a positive medical indication. Further, there should be no promise or guarantee that the patient will be sterilized as the result of the procedure undertaken.

The individual physician must secure consent to perform a postmortem examination. This, too, should be in writing [7] and sufficiently comprehensive to allow the removal and taking away of tissue if such is to be done.

The trend of the cases in recent years indicates that it is extremely unwise to pursue a course of treatment in itself hazardous or capable of producing harmful effect without securing a written statement from the patient, or from someone legally responsible for the patient—a statement which clearly expresses understanding of and consent to the special treatment.

FAILURE TO USE RECOGNIZED DIAGNOSTIC AIDS

There are a large number of malpractice actions in the law reports which may be classified under the general heading of "Insufficient Treatment Cases." In every field of medical practice there are cases illustrating "insufficient care": the failure to make a blood count, a Wassermann, a pregnancy test, a culture, a smear, a urinalysis, a stool examination, an x-ray, original or follow-up; failure to make a complete diagnosis or overlooking a reasonably determinable condition; failure to utilize an indicated prophylactic measure (diphtheria, tetanus, etc.); the failure to give instructions, to follow up the original treatment or operation, to institute measures to protect contacts, etc., etc.

Failure to use the x-ray at all, or failure to make sufficient use of the x-ray, has been the chief allegation in many malpractice actions. Whenever a fracture is present which was not diagnosed and no x-rays were taken, the conduct of the attending physician is likely to be condemned as not coming within the standard of good practice.[8] Whenever a bad result, deformity or limitation of motion occurs, the defense is immeasurably strengthened by the possession of a series of x-rays taken at intervals during the progress of the case. Whenever a patient refuses to have an x-ray made, the physician should fortify himself with the strongest written evidence. X-ray records, as well as the entire case record, should be carefully preserved beyond the time during which a malpractice action may be brought.

The statute of limitations provides the period of time after which specified actions may not be brought. The time provided varies greatly in the several states. A physician should wisely inform himself of the situation in his own state.

3. There is a legal presumption that a letter mailed has been received by the addressee; but there is no presumption that a letter has been mailed.

4. Statutory exception: In California a female of the age of 18 or more who is or has been married is an adult for the purpose of this consent.

5. Under Eugenic Sterilization Statutes.

6. 48 C. J. 1131; Jackovach v. Yocum (Iowa), 237 N. W. 444.

7. In California, and several other states, it is criminally illegal for any person to perform an autopsy without having first obtained the written authorization of the coroner or other authorized public officer or of the person who has the right of disposition of the body.

8. "The failure to make use of x-ray as an aid to diagnosis in cases of fracture amounts to a failure to use that degree of care and diligence ordinarily used by physicians of good standing in the community and the court, in absence of expert testimony, may take judicial notice of such fact." Agnew v. City of Los Angeles (Cal.), 218 Pac. (2d) 66.

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OBLIGATIONS TO PATIENTS

To summarize, the physician who would understand his legal obligations, responsibilities, and duties to his patient, must constantly bear in mind the following fundamental obligations:

1. The physician must possess the degree of skill commonly possessed by other reputable practitioners in the same field of practice.

2. He must exercise the degree of care, diligence, and judgment commonly and ordinarily exercised by other reputable members of his profession in similar circumstances.

3. He must keep abreast of progress and follow good practice, common practice, in diagnosis and treatment; he must not experiment.

4. He must not neglect or abandon his patient; he must proceed diligently, without unnecessary delay.

5. He must give his patient sufficient attention and must utilize the indicated diagnostic aids.

6. He must find or anticipate any condition reasonably determinable or reasonably likely to develop.

7. He must obtain legal consent to operate and to perform an autopsy.

8. He must give proper instructions (that is, instructions consistent with the standard of practice) for the care of the patient in his absence, and for the protection of those coming in contact with the patient.

9. He must fulfil the terms of a special contract if he makes one.

The foregoing directions for reducing and avoiding the instigation of malpractice suits will not, of course, guarantee that a physician will not be sued unjustly; for already malpractice may be regarded as a contagious disease of the social body. There are several major reasons for this condition, but two are paramount: (1) the winning of a suit inevitably encourages the filing of others as patients become increasingly "suit conscious"; and (2) such suits are difficult to defend, and the knowledge of how best to conduct such a defense is not sufficiently widespread. The inter-relationship of these two points will be obvious; for each successful defense of an unjust suit will serve as a discouragement to the filing of others. But the second of these causes of high malpractice incidence—the difficulty of conducting a defense—is dangerously enlarged by many physicians themselves. Large numbers of medical men are naive enough to believe that their patients would never file such suits and that no precautions need be taken; and yet such precautions are the only assurance of the best possible defense in the event of a suit. The most vulnerable physicians are those who know that they are maintaining at least an average standard of practice and who are therefore (and blindly) assuming that they will not be sued. This discussion is concerned with *unjust* claims; no doctor who is actually guilty of malpractice should be allowed to go free of penalty. Meritorious claims should be settled out of court—preferably before a suit has been filed.

PROMPT ATTENTION SHOULD BE GIVEN TO CLAIMS

Another too frequent hindrance to an adequate defense is delay in the investigation of claims; such delay is highly disadvantageous to the preparation of a defense. As a final word of warning that the physician may need every available precaution, one must consider the conditions under which most cases are heard. They are tried before juries made up of lay persons, and it is a truism that no one can say what a jury will do. This is particularly true of malpractice cases, for certainly lay jurors can not be expected to understand complex medical facts. How does a jury arrive at a decision when two expert witnesses testify that the defendant's conduct of the case did not meet the required standard, and two others declare that what the defendant did was consistent with the usual and ordinary practice in the community?

To physicians who have had little or no experience with the law and to lawyers who have little or no medical knowledge, the problem of adequately defending the unjust malpractice case seems insurmountable. And it is true that far too many such cases have been lost simply through poor defense. This is an aspect of the problem which needs a great deal more attention, particularly in areas which have become virtual "hot beds" of nonmeritorious malpractice claims. At all times and to all physicians, there should be available expert advice on problems relating to the physician-patient relationship.[9] Whenever a threat is made against a physician, a carefully prepared procedure should be put into effect. Unjustified claims should be contested as thoroughly as possible. In such cases, it is sheer folly to compromise, on the theory that a slight settlement would be less expensive than the cost of defense. Such a course simply serves as an encouragement to others whose claims are not justified. This shortsighted view is largely responsible for the rapid increase in the number of malpractice claims in some sections of the country. If cases based upon unjust or absurd claims are permitted to receive even a slight profitable return, there will be an incentive to bring more of them.

BE SLOW TO COMPROMISE

It is a great temptation to a doctor to rid himself of a nuisance claim by making a small settlement. The unfavorable publicity, the loss of time, and the mental and emotional strain involved in defending a malpractice suit may lead the physician to compromise. But, as is so often true, the easiest way out of a situation is seldom the best. For the sake of both himself and his colleagues, the doctor should make a determined opposition to an unjustified claim.

A LIST OF "COMMANDMENTS" IN MALPRACTICE PREVENTION

In the final analysis, it is the physician himself who is responsible for the continuing existence of the vicious malpractice situation. The physician has generally been satisfied to pay his professional liability insurance premiums and thereafter to sit back complacently, doing nothing until he becomes a target for a malpractice claim. He must be brought to realize that his money payment is only a part of his insurance premium; a much more important part is his contribution of time, of study, and of putting into effect all possible measures to safeguard himself and his colleagues.

Prevention is the best defense against malpractice. Listed below are the 23 malpractice prophylaxis "commandments":

1. The physician should care for every patient with scrupulous attention to the requirements of good medical practice.

2. The physician must know his legal duty to the patient.

3. The physician must avoid destructive and unethical criticism of the work of other physicians.

4. The physician should keep "ideal" medical records in every case: records that would be presentable when offered in court; records that clearly show what was done and when it was done; records that clearly indicate that nothing was neglected and that the care given met fully the standard demanded by the law. If any patient discontinues treatment before he should, or fails to follow instructions, the record should show it; a good method is to file a carbon copy of the letter which advises the patient against the unwise course.

5. The physician should be careful to avoid making any statement which constitutes or which might be construed as an admission of fault on his part. Such an admission, which is usable against the physician, might be made to a third party as well as to the patient at any time before the trial. Such an admission may be made by an agent or employee of the physician during the course and within the scope of the employment. It is important to instruct employees to make no statements.

6. The physician should exercise tact as well as professional ability in handling his patients. A proper professional manner and a sound attitude should be maintained at all times toward both the patient and the patient's family. The attentive physician may early sense some unsatisfactory and disturbing under-current which, by the institution of protective measures, may be prevented from developing into something much more unpleasant. Thus, if the patient is not doing well, consultation may be suggested; if the patient is dissatisfied or complaining, or if the family's attitude indicates dissatisfaction, consultation should be demanded. The use of a consultant affords, in any case, great protection against a malpractice claim.

7. The physician should refrain from overoptimistic prognoses and should avoid promising too much to the patient.

9. Regan, L. J.: Doctor and Patient and the Law, St. Louis, The C. V. Mosby Company, 1949, chap. 20.

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8. The physician should advise his patients of any intended absence from practice and should recommend, or make available, a qualified substitute.

9. The physician should unfailingly secure written consent for operation and for autopsy.

10. The physician should carefully supervise assistants and employees and take great care in the delegation of duties to them.

11. The physician should have some knowledge of the statute of limitations and of its significance.

12. In his selection of patients the physician should limit himself to such fields as are well within his qualifications. He should keep abreast of progress in the medical profession.

13. The physician should keep inviolate all confidential communications.

14. The physician should frequently check the condition of his equipment and make use of every available safety installation.

15. In the treatment of the patient the physician must not experiment.

16. The physician must be careful to render sufficient care to his patient in general instructions, frequency of visits, clinical and roentgen ray laboratory investigations and the like. Moreover, every precaution should be instituted for the protection of those caring for the patient and of all other contacts.

17. The patient must not be abandoned. The physician-patient relation can be terminated without liability only in certain ways and under certain conditions.

18. The physician should never reveal that he carries professional liability insurance. Except on the recommendation of his legal adviser, he should never write a letter or make any statement with reference to a malpractice claim. Immediately on being advised of even the possibility of suit, he should consult with his attorney.

19. The physician should arrive at an understanding in the matter of fees. Misunderstanding in this matter, particularly when the question of excessive fees arises, contributes an avoidable element of risk.

20. The physician should secure legal advice if he is called to attend a coroner's inquest as a witness in a case in which he has been in professional attendance.

21. The physician should realize that because of the possibility of error in transmission, it is dangerous to telephone a prescription.

22. The physician should realize that it is hazardous to sterilize any patient except when a medical indication exists.

23. Except in actual emergency, the physician should not examine a female patient unless a third person is present. There is no more serious or destructive charge than that of undue familiarity; and the only way to avoid claims of this sort seems to be to have some one else present during all examinations.

CONCLUSIONS

There must be recognition of malpractice as a problem; that the conditions created by it are harmful to the physician and injurious to the public; and that action must be taken to correct it.

The public should be informed as to (1) what constitutes malpractice, (2) how really few cases of actual malpractice occur, and (3) the major degree of responsibility which the individual has in the maintenance of his own health.

Physicians must learn what they may do to safeguard themselves, and must put into effect every possible precaution against an unjust malpractice accusation.

ADDENDA

I. CONSENT TO OPERATION

Place .....

Date .....

1. I hereby authorize and direct Dr. .....
to perform the following operation upon me.....
.....
.....
and to do any other procedure that (their) (his) judgment may dictate during the above operation.

2. I understand that the surgeon (surgeons) will be occupied solely with the surgery, and that the administration and maintenance of the anesthesia are independent functions, and will be in charge of Dr. ..... I consent to the administration of such anesthetic, or anesthetics, as Dr. ..... may deem advisable in my case.

3. It has been explained to me that I may be sterile as a result of this operation, although no such result is warranted or guaranteed. I understand what the term sterility means and, in giving my consent to the operation, I have in mind the possibility (probability) of such a result.

A.M. Signed .....

Hour ..... P.M. Witness .....

4. I join in authorizing the performance, upon my (husband) (wife), of the surgery consented to above. It has been explained to me that, as a result of the operation, my (husband) (wife) may be sterile.[1]

Date ..... Signed .....

A.M. Witness .....

Hour .....

P.M.

1. Cross out paragraphs not applicable to particular case.

II. CONSENT TO OPERATION UPON MINOR

Place .....

Date .....

1. I (we) being the parent(s), guardian, custodian of a minor of the age of....., do hereby authorize and request Dr. .....
..... to perform such surgical operation on the person of said ....., a minor, as the judgment of said Dr. ..... may dictate.

2. I (we) also authorize and request the employment of such anesthetic or anesthetics as may be deemed suitable in the judgment of the said Dr. ....., or in the judgment of the anesthetist selected to administer the anesthetic or anesthetics in this case.[2]

2. A similar consent form may, and should, be used in the case of a patient who is incompetent; signed by guardian, custodian, or other person legally responsible for the incompetent.

A.M. Signed .....( )

Hour .....P.M. .....

Witness .....

III. CONSENT TO OBSERVERS AND/OR PHOTOGRAPHS AND/OR TELEVISING

In the interests of science and the furtherance of medicine, I, the undersigned, do hereby consent to and authorize..... Hospital, and the Operating or Treating Surgeon and such doctors as may be assisting him, to examine and operate or treat me in the presence of other than the usual surgical staff.

I further authorize and consent to the taking of photographs and such subsequent use thereof as may be deemed advisable by said hospital and/or doctor, or doctors.

I further authorize and consent to the televising of any operative or other procedure performed or carried out upon me.

Dated ..... Signed .....

Witness ..... Witness .....

IV. PATIENT FAILS TO CARRY OUT ADVICE

Note. When a patient neglects or fails to carry out advice, it is desirable to have the facts established in writing. It may be wiser to withdraw from the case (See VII). This is a matter for the judgment of the physician in the particular case.

SAMPLES [3]

3. Substance of letter to patient to be changed to fit the particular facts and circumstances. Carbon copy, with proof of mailing of original written thereon, to be filed with medical case record.

Place .....

Date .....

A.

Name of Patient
Address

Dear Mr. .....:

At the time of my examination of your ankle this afternoon, I advised you of the desirability of having x-rays made. This you refused to do.

Upon your insistence that I treat your ankle and foot, without benefit of x-rays, I agreed to do my best in the circumstances, but as I advised you this afternoon, and must repeat now, I cannot establish, without x-rays, whether or not you have incurred a fracture.

In your own interest, I urge that you have an immediate x-ray study made of your foot and ankle.

Yours very truly,

B.

Dear Mrs. .....:

Upon the history you gave me and my findings on examination, both of this date, I am not able, as I told you at the time of your visit, to rule out pregnancy as the cause of the vaginal bleeding of which you complain.

You have told me that you will not submit to a pregnancy test. I again now advise you of its desirability. I hope you will come in tomorrow morning prepared, as I instructed you, to have the test made. If you continue to refuse to submit to this test, it will be necessary to have a consultant see you tomorrow, if I am to continue to advise you.

Yours very truly,

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C.

Dear Mrs. .....:

When, in response to your call today, I saw your husband at your home, I told you my opinion was that he is very seriously ill with pneumonia, and that he should be immediately hospitalized. You refused to permit me to have him removed to the hospital. I told you that I am willing to do the best I can for him under the circumstances, but that he could be better cared for and he would be safer, with less likelihood of complication, in the hospital.

Your husband's condition is such that the matter cannot be discussed with him, so I hope that you will now, after giving the matter more thought, authorize his removal to the hospital.

Yours very truly,

D.

Dear Mrs. .....:

You brought your seven-year old boy in today for me to see. He has a deep, penetrating wound on the sole of his foot, apparently resulting from his stepping on a nail. You thought that it had been received in a neighboring stable.

I advised you that the boy should immediately be given an injection of tetanus antitoxin. You refused to permit me to administer this to him, stating that you had heard of two children who had severe reactions following such prophylactic treatment.

I told you that I would make a preliminary test which would warn us of the likelihood of severe reaction, but that I could not guarantee that result or any result. You reiterated your refusal.

I cannot give the boy this treatment, or any treatment, without your consent. I urgently recommend that you permit me, or some other physician of your choice, to administer a preventive dose of tetanus antitoxin to your boy without further delay.

Yours very truly,

V. PATIENT FAILS TO KEEP APPOINTMENT

SAMPLES [4]

4. When a patient fails to keep an appointment, or discontinues treatment before he should, it is desirable to send him a letter, incorporating the pertinent facts and the recommendations. File a carbon copy, endorsed with a certificate of mailing, with medical case record. Registered mail may be used.

Place .....

Date .....

A.

Name

Address

Dear Mr. .....:

My records indicate that you failed to keep your appointment of ..... (date), and that you have not made any subsequent appointment or appearance in the office.

In your own interest, may I call to your attention the fact that further professional attention is, in my opinion, definitely needed. If there is some reason why you prefer not to return to this office, I urge that you immediately seek other competent professional care. I shall be glad to give the benefit of my knowledge of your case to your subsequent physician, should you elect to receive the needed attention at other hands.

Yours very truly,

B.

Dear Mrs. .....:

You have not returned, as arranged, since, at your request, I examined you on last Friday.

The history you gave of "spotting" between periods over the last several months, and my findings on examination, which I related to you, are of such significance that, as I endeavored to impress upon you when I made an appointment for you to return with your husband, I must urge upon you the advisability of having immediate medical attention.

If you do not wish to return to me, you should consult another physician at once.

Yours very truly,

C.

Dear Mrs. .....:

You failed, again, today to appear in accordance with your appointment at the Radiologist's office so that a check-up x-ray could be made of your fractured wrist.

I have previously urged upon you the necessity of having your cooperation to improve the likelihood of a favorable result.

You should not be heard to complain of the end result, if it is not satisfactory, when you refuse or neglect to follow the advice of your physician.

I now request that you appear at my office at ten o'clock tomorrow morning. I am arranging to have x-rays made at that time and to have a specialist in orthopedic surgery see your arm.

Yours very truly,

VI. PATIENT DISCHARGES PHYSICIAN FROM CASE [5]

5. If a physician justifies his failure to continue in attendance upon a patient upon either his having withdrawn from the case or of having been discharged by the patient, the burden of proof of such contention is upon him—hence the desirability, if not the actual necessity, of having written evidence available.

Dear Mr. or Mrs. .....:

This is confirmation, and my acknowledgment, of the fact that you have, as of this date, discharged me from further professional attendance upon you in your current illness.

Should you desire, I shall be glad to cooperate with the physician you now call, in supplying him with such information as I have gained in respect to your case.

Yours very truly,

VII. PHYSICIAN WITHDRAWS FROM CASE

Note. A physician may withdraw from attendance upon a patient, but he must give reasonable notice of his intention to do so and must allow the patient reasonable time and opportunity to fill his place. If the fact, whether a physician did withdraw from professional attendance upon a patient, became an issue in the case, the burden of proof falls upon the physician. For this reason, it is desirable that written evidence be available.

It is a serious question of judgment, whether, when a patient fails to cooperate or refuses to follow advice, the physician should continue on the case. It is recommended that, if the physician decided to continue to care for an uncooperative patient, a patient, who, for example, refuses to have an indicated x-ray study made, he should demand and require consultation.

SAMPLES [6]

6. Letters should be sent and carbon copy filed. The wording should be simple and direct, but the intent and meaning must be clear and certain.

Place .....

Date .....

A.

Name

Address

Dear Mr. .....:

You have repeatedly failed to follow my advice and recommendations.

I am therefore advising you of my intention to withdraw from further professional responsibility in connection with your case. To allow you a reasonable opportunity to secure another physician, I shall be available, at your request, to render you service for three days from your receipt of this letter, but not thereafter. In this period of time, in this community of several hundred physicians, you can readily fill my place.

I shall be glad to give, to any reputable physician of your choice, the benefit of such knowledge as I have gained of your case.

Yours very truly,

B.

Dear Mr. .....:

You consulted me this afternoon in connection with an injury to your foot and ankle. At that time, upon your refusal to have x-rays made of the injured area, I advised you that I could not undertake to render professional service to you.

So that there may be no misunderstanding, I am confirming these facts in writing.

Yours very truly,

C.

Dear Mrs. .....:

As I told you this morning, I cannot longer continue to be professionally responsible for the care of your little boy. This decision is necessitated by the fact that you have repeatedly refused to permit me to make the detailed and thorough study of his condition which I regard as indicated and vital.

Please secure other medical attention at once. In the meantime, and for a reasonable time, I shall remain available, at your request, to render any routine or emergency service that may be required.

I shall, of course, be glad to offer to Tommy's new physician the knowledge of his case which I have been permitted to acquire.

Yours very truly,

D.

Dear Mrs. .....:

You failed to keep your appointment this week.

At the time you received your injection last week a portion of the needle broke off in your tissues. You were at once advised of this accident. As I told you, after preliminary search, I was unable to recover the broken piece without anesthesia and incision, and recommended that localization studies be made prior to undertaking definitive search.

I again recommend that procedure and will make arrangements at your request and responsibility.

Yours very truly,

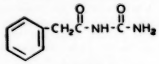
COUNCIL ON PHARMACY AND CHEMISTRY

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies. A copy of the rules on which the Council bases its action will be sent on application.

R. T. STORMONT, M.D., *Secretary.*

Phenacemide.—Phenurone (Abbott).—$C_9H_{10}N_2O_2$.—M.W. 178.19.—Phenylacetylurea.—The structural formula of phenacemide may be represented as follows:



Actions and Uses.—Phenacemide is a synethetic anticonvulsant with only minor sedative action. In experimental animals the drug shows effectiveness against electroshock seizures and convulsions produced by pentylenetetrazole. Large doses produce marked ataxia and loss of reflex activity. Studies in animals also indicate that the liver plays a major role in the destruction of the drug.

Phenacemide is used in the treatment of pyschomotor epilepsy, grand mal and petit mal epilepsies and in the management of mixed seizures. *The drug has serious side effects. Personality changes (including attempts at suicide and toxic psychoses), hepatic damage and bone marrow depression, as evidenced by leucopenia and aplastic anemia, have followed administration of the drug. It should be employed only by physicians experienced in the treatment of epilepsy and only in patients whose seizures are difficult or impossible to control with other recognized anticonvulsants.*

Phenacemide should not be employed in patients with evidence of liver dysfunction and should be used with caution in patients with histories of personality disorders or sensitivity to drugs. It may be advisable to hospitalize such patients for observation during the first weeks of treatment. Psychiatric signs such as withdrawal and loss of interest indicate onset of serious personality changes. Careful clinical observation throughout the course of therapy is especially important during the first six months; the physician must be constantly alert for such symptoms as anorexia, nausea, vomiting, general malaise, fever, rash or jaundice, as they may be early signs of liver damage or blood dyscrasia. Anorexia, nausea and vomiting may be due to only gastrointestinal distress, but if persistent may be of more serious significance. Patients should be instructed to report such signs immediately. Blood counts and liver function tests should be made on all patients preliminary to and regularly during treatment.

Dosage.—Phenacemide is administered orally and the dose determined according to the response of the patient and the degree of control already obtained with other anticonvulsant agents. It may be given in conjunction with phenobarbital, diphenylhydantoin sodium, trimethadione or paramethadione. It is recommended that when some control has been achieved with other medication, this should be continued and phenacemide added at a dosage of 0.5 gm. three times daily with meals. The dose should be increased gradually to the minimum required for adequate control or until limiting side effects develop. The action of an average dose appears to last for three to five hours. If control by phenacemide alone is anticipated, other medication can be reduced; but if a combination of phenacemide with other drugs permits better control, or allows control with lower dosage of phenacemide or less disturbing side effects, the combination of medication should be continued. Doses as small as 0.25 gm. three times daily may be adequate in some cases. The average total daily adult dose seldom exceeds 2 to 3 gm. For children 5 to 10 years of age, approximately half the adult dose is recommended. The maintenance dose should be the smallest amount which will adequately control seizures. Personality disturbances, signs of liver damage, rash or depression of the blood count, particularly of erythrocytes and polymorphonuclear leucocytes, are indications for withdrawal. Cautious reinstitution of therapy may be considered when improvement occurs.

Tests and Standards.—

Physical Properties: Phenacemide is a white to creamy white, odorless, tasteless, crystalline solid. It melts between 212.0 and 216.0 C. It is slightly soluble in alcohol, benzene, chloroform and ether; and is very slightly soluble in water.

Identity Tests: To 5 mg. of phenacemide in an evaporating dish add 2 ml. of 1% potassium nitrate in sulfuric acid. Heat the mixture on a steam bath for 30 min., then add 10 ml. of water and 0.2 gm. of zinc dust. Heat the mixture on a steam bath for 30 min. Cool, dilute to 25 ml. and filter. Transfer 1 ml. of the filtrate to a test tube; add 1 ml. of 20% toluenesulfonic acid, 8 ml. of water and 1 ml. of 0.1% sodium nitrite; and allow the mixture to stand 3 min. Add 0.5 ml. of 0.5% sodium sulfamate and allow the mixture to stand 2 min. Finally add 5 ml. of 1:250 N,N-dimethyl-1-naphthylamine in alcohol and allow the mixture to stand 15 min.: the solution becomes light purple.

Using about 0.4 gm. of phenacemide, prepare phenylacetic acid as directed in the assay through, "Evaporate the extract to dryness, blow off the last traces of chloroform . . . ." Recrystallize the residue from water and dry it over phosphorus pentoxide in a vacuum for 24 hours: the phenylacetic acid obtained melts between 75.0 and 77.0 C.

Purity Tests: Dry about 1 gm. of phenacemide, accurately weighed, for 4 hours at 105 C.: the loss in weight is not more than 1.0%.

Ignite about 1 gm. of phenacemide, accurately weighed: the residue is not more than 0.05%.

Assay: (Phenylacetic Acid) Transfer about 0.4 gm. of phenacemide, accurately weighed, to a 100 ml. round-bottomed flask. Add 50 ml. of water and 8 ml. of sulfuric acid, and reflux the mixture for 1 hour on a hot plate. Transfer the contents of the flask to a 250 ml. separatory funnel, and wash the condenser and flask with three 15 ml. portions of chloroform. Add the washings to the separatory funnel and extract the phenylacetic acid first with the combined chloroform washings (45 ml.) and then with five 20 ml. portions of chloroform. Filter the combined chloroform extracts through cotton and wash the filter thoroughly with 20 ml. of hot chloroform. Evaporate the extracts to dryness, blow off the last traces of chloroform and dissolve the residue in 25 ml. of alcohol. Titrate the solution with 0.1 *N* sodium hydroxide using phenolphthalein T.S. as an indicator. Each milliliter of 0.1 *N* sodium hydroxide is equivalent to 0.01361 gm. of phenylacetic acid and 0.01782 gm. of phenacemide. The amount of phenylacetic acid present is not less than 74.9 nor more than 77.9%, equivalent to not less than 98.0% nor more than 102.0% of phenacemide.

Dosage Forms of Phenacemide

TABLETS. *Identity Tests:* Using an amount of crushed tablets equivalent to about 0.4 gm. of phenacemide, prepare phenylacetic acid as directed in the assay through, "Evaporate the extract to dryness, blow off the last traces of chloroform . . . ." Recrystallize the residue twice from water and dry it over phosphorus pentoxide in a vacuum for 24 hours: the phenylacetic acid obtained melts between 75.0 and 77.0 C.

Assay: (Phenylacetic Acid) Weigh 20 tablets and grind them. Accurately weigh the equivalent of about 0.4 gm. of phenacemide and transfer it to a 100 ml. round-bottomed flask. Proceed as directed in the assay for phenylacetic acid in the monograph for phenacemide starting with "Add 50 ml. of water and 8 ml. of sulfuric acid . . . ." The amount of phenacemide present is not less than 95.0% nor more than 105.0% of the labeled amount.

Tablets Phenurone: 0.5 gm. U. S. Trademark 522,257. Abbott Laboratories, North Chicago, Ill.

Aminophylline-U.S.P. (See New and Nonofficial Remedies 1951, p. 297).

Solution Aminophylline: 10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter. Testagar & Company, Inc., Detroit.

Solution Aminophylline with Benzyl Alcohol 2%: 2 cc. ampuls. A solution containing 0.25 gm. of aminophylline in each cubic centimeter. Testagar & Company, Inc., Detroit.

Calcium Levulinate-N.F. (See New and Nonofficial Remedies 1951, p. 408).

Solution Calcium Levulinate: 10 cc. ampuls. A solution containing 0.1 gm. of calcium levulinate in each cubic centimeter. The S. E. Massengill Company, Bristol, Tenn.

Chorionic Gonadotropin (See New and Nonofficial Remedies 1951, p. 359).

Lyophilized Chorionic Gonadotropin: 10 cc. vials containing 5,000 I.U. Powdered preparation of chorionic gonadotropin which, when diluted with the accompanying 10 cc. (vial) of sterile distilled water containing 0.5% phenol, makes a solution having a potency of 500 I.U. in each cubic centimeter. U. S. Patent 1,910,298. B. F. Ascher & Company, Inc., Kansas City, Mo.

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Dihydroxy Aluminum Aminoacetate (See New and Nonofficial Remedies 1951, p. 311).

Tablets Robalate: 0.5 gm. A. H. Robins Company, Inc., Richmond, Va.

Heparin Sodium-U.S.P. (See New and Nonofficial Remedies 1951, p. 213).

Solution Heparin Sodium (High Potency): 10 cc. vials. A solution containing 5,000 U.S.P. units (approximately 50 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent phenol. Testagar & Company, Inc., Detroit.

Mephenesin (See New and Nonofficial Remedies 1951, p. 165).

Tablets Myoxane: 0.5 gm. B. F. Ascher & Company, Inc., Kansas City, Mo.

Meth-Dia-Mer-Sulfonamides (formerly Sulfadiazine-Sulfamerazine-Sulfamethazine Mixture. See New and Nonofficial Remedies 1951, p. 103).

Suspension Truozine with Sodium Citrate (Flavored): 473 cc. bottles. A suspension containing 20 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.1 gm. of sodium citrate in each cubic centimeter. Abbott Laboratories, North Chicago, Ill.

Dulcet Tablets Truozine: Each tablet contains 0.1 gm. each of sulfadiazine, sulfamerazine and sulfamethazine. U. S. Trademark 500,527 (Dulcet). Abbott Laboratories, North Chicago, Ill.

Tablets Truozine: Each tablet contains 0.167 gm. each of sulfadiazine, sulfamerazine and sulfamethazine. Abbott Laboratories, North Chicago, Ill.

Pyrilamine Maleate (formerly Pyranisamine Maleate. See New and Nonofficial Remedies 1951, p. 13).

Tablets Stangen Maleate: 25 mg. and 50 mg. Physicians' Drug & Supply Company, Philadelphia.

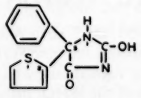
Terramycin Hydrochloride (See New and Nonofficial Remedies 1951, p. 136).

Elixir Terramycin Hydrochloride (Oral Drops): 10 cc. dropper bottles. A flavored alcohol solution containing the equivalent of 0.2 gm. of terramycin as the hydrochloride in each cubic centimeter. The terramycin hydrochloride and diluent are packaged together in separate containers to be mixed before use. Chas. Pfizer & Company, Inc., Brooklyn, N. Y.

Vitamin B_{12} (See New and Nonofficial Remedies 1951, p. 454).

Solution Crystalline Rametin with Benzyl Alcohol 1.5%: 10 cc. vials. A solution containing 10 or 15 micrograms of Vitamin B_{12} in each cubic centimeter. The Bio-Ramo Drug Company, Baltimore.

Phethenylate.—Thiantoin (Lilly).—5-Phenyl-5-(2-thienyl)hydantoin.—$C_{13}H_{10}N_2O_2S$.—M.W. 258.29.—The structural formula for phethenylate may be represented as follows:



Actions and Uses.—Phethenylate is employed for the same purpose as its sodium salt. See the monograph for Phethenylate Sodium.

Dosage.—Phethenylate is prescribed in doses equivalent to those for phethenylate sodium. See the monograph for the sodium salt.

Tests and Standards.—

Physical Properties: Phethenylate is a white, tasteless, hygroscopic, microcrystalline powder with a slight, characteristic odor. It melts between 255 and 259°. One gram of phethenylate is soluble in about 35 ml. of alcohol. It is slightly soluble in chloroform and ether, and very slightly soluble in benzene and water. The pH of the saturated aqueous solution is about 6.5.

Identity Tests: To a dispersion of about 20 mg. of phethenylate in 3 ml. of thiophene-free benzene add a solution of about 10 mg. of isatin in 1 ml. of sulfuric acid, shake the mixture vigorously for about 1 min. and allow the tube to stand for 30 min.: the acid layer becomes a stable brown-green. Run a blank on the reagents: no change in color occurs in the acid layer. *(The test proves the presence of the thienyl group and distinguishes phethenylate from diphenylhydantoin.)*

Purity Tests: Dissolve the residue from the ignition of phethenylate, as described later, in 20 ml. of hot water. Cool the solution, add 2 ml. of diluted acetic acid and make up to a total volume of 25 ml. Run a heavy metals test as directed in *U. S. P. XIV*, p. 717: no more turbidity develops than in a control containing 30 γ of lead.

Dry about 1 gm. of phethenylate, accurately weighed, for 24 hours at 105°; the loss in weight is not more than 1.0 per cent.

Char about 1 gm. of phethenylate, accurately weighed, over a low flame. Cool the charred mass, then add 1 ml. of sulfuric acid and continue ignition until no carbon remains: the residue is not more than 0.10 per cent.

Assay: (Phethenylate) With gentle heat, dissolve about 0.5 gm. of phethenylate, accurately weighed, in 50 ml. of alcohol and 45 ml. of water contained in a 250 ml. Erlenmeyer flask. Titrate the dissolved acid with 0.1 *N* sodium hydroxide using thymolphthalein T. S. as an indicator. Run a blank titration on the alcohol. Each milliliter of 0.1 *N* sodium hydroxide consumed is equivalent to 0.02583 gm. of phethenylate. The amount of phethenylate present is not less than 97.0 nor more than 103.0 per cent.

(Nitrogen) Carry out a Kjeldahl or a semi-micro Kjeldahl determination as directed in *U. S. P. XIV*, p. 740. The amount of nitrogen present is not less than 10.5 nor more than 11.2 per cent, equivalent to not less than 97.0 nor more than 103.0 per cent of phethenylate.

Dosage Forms of Phethenylate

SUSPENSION: *Identity Tests:* Shake the suspension thoroughly. Extract a volume of suspension equivalent to about 0.5 Gm. of phethenylate with four 25 ml. portions of ether. Evaporate the combined ether extracts on a steam bath and dry the residue at 105° for 1 hour. On a dispersion of about 20 mg. of the dried residue in 3 ml. of thiophene-free benzene carry out the identity test described in the monograph for Phethenylate.

Assay: (Phethenylate) Thus far, no satisfactory chemical method has been developed for the assay of this dosage form due to interference from other ingredients. The manufacturer utilizes the following infrared spectroscopic method: Shake the suspension thoroughly. Transfer to a 125 ml. separatory funnel an amount, accurately measured, equivalent to about 50 mg. of phethenylate. Add 5 ml. of 0.1 *N* hydrochloric acid and then 25 ml. of water. Extract the solution thus formed with exactly 50 ml. of chloroform. Draw off the chloroform extract into a small glass stoppered flask containing a little anhydrous sodium sulfate. Place the dried extract in a rocksalt cell with a 1 mm. light path. Record the spectrum between 5.4 and 5.8 μ on a Baird Infrared Recording Spectrophotometer A, using chloroform in a 1 mm. reference cell as a blank. The percentage of phethenylate present = 100 (absorbancy at 5.72 μ − 0.016) ÷ 0.407, where 0.016 is a correction for absorption at 5.72 μ by substances other than phethenylate and 0.407 is the absorption at 5.72 μ of a chloroform solution containing 1 mg./ml. of phethenylate. The amount of phethenylate present is not less than 90.0 nor more than 110.0 per cent of the labeled amount.

Oral Suspension Thiantoin: 475 cc. bottles. A suspension containing approximately 24 mg. of phethenylate (equivalent to 26 mg. of phethenylate sodium) in each cubic centimeter. Eli Lilly & Company, Indianapolis.

COUNCIL ON PHYSICAL MEDICINE AND REHABILITATION

COUNCIL APPOINTMENTS

The Board of Trustees has appointed Dr. Ralph E. DeForest, Rochester, Minn., as Secretary of the Council on Physical Medicine and Rehabilitation. A graduate of Wayne University College of Medicine, Dr. DeForest also holds a master of science degree in physical medicine and rehabilitation from the University of Minnesota, where he did research on the effects of ultrasound on growing bone. He has been a fellow in orthopedic surgery and in physical medicine and rehabilitation at the Mayo Foundation and has served with the Army Medical Corps in occupied Germany. His appointment became effective August 1. Howard A. Carter, former secretary of the Council; has been made director of biophysical investigation and associate secretary of the Council. Dr. Frederick T. Jung, assistant secretary of the Council, has been appointed director of the new physical laboratory.

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION
535 N. DEARBORN ST. . . . . CHICAGO 10, ILL.
Edited by . . . . . AUSTIN SMITH, M.D.
Associate Editor . . . . . JOHNSON F. HAMMOND, M.D.
Editor for Medical Literature Abstracts . GEORGE HALPERIN, M.D.

Subscription price . . Fifteen dollars per annum in advance
Cable Address . . . . . "Medic, Chicago"

THE USE OF NEW DRUGS

Until recent years the use of drugs has been accompanied by comparatively few worries concerning toxic reactions. An overdose might kill, but usually the difference between the average dose and a fatal dose was large. Not often did a patient react unexpectedly, except when a certain group of drugs was used or unless the patient was unusually sensitive to a drug. Today, however, the situation is different. Potent and specific drugs have been developed; their effects are sometimes unpredictable, and in some cases death has followed their use. Physicians thus are asked sometimes whether modern drug therapy is safe, whether the probable outcome is worth the risk. Perhaps the simplest way to answer such questions is to say that modern drug therapy sometimes produces seeming miracles, that without it countless lives would be lost and untold suffering continued. At the same time it can be pointed out that, with adequate precautions and safeguards, the use of drugs is not normally a dangerous procedure. Of course, physicians must admit more to themselves if accidents are to be prevented. They must appreciate that unexpected and unfavorable reactions can occur in spite of exhaustive research prior to the release of a new drug, that individuals react differently and often unpredictably, and that sometimes truly questionable drugs must be used when heroic measures are indicated. The careful physician uses a drug only when he knows what it can be expected to do and when he is convinced the patient needs it. He then is willing to admit that, while a risk may be involved, the risk is slight when compared to the comfort the drug provides. No one would deny the use of the sulfonamides or the antibiotics because they can cause worrisome reactions. Their value is too well demonstrated to warrant their discard because of clinical disturbances in some patients. Physicians versed in the use of drugs realize that far more harm is done by the misuse of drugs than by the occasional use of a drug that carries with it some risk.

Elsewhere in THE JOURNAL (page 17) is a report on the use of a new drug (phenacemide) for epilepsy. This drug can be dangerous unless properly employed and even then is not completely free of danger. One might ask, then, whether the drug should be released for general use. The answer lies, in part, in careful supervision of the administration of the drug, in the medical profession's employing it only after it is fully informed, and in restricting the sale to prescription use. The answer also lies, in part, in consideration of the value of the drug: Does its usefulness outweigh its disadvantages? To determine this, the prescriber must keep in mind the amount of research that first was compiled by able investigators, the seriousness of epilepsy, and the reactions that have always attended drug therapy for epilepsy. Even the best known drugs, including those in New and Nonofficial Remedies, have not been free of toxic properties. If the prescriber is convinced that the drug has special usefulness and that he understands the actions and uses, he can use it; if he is not convinced, he should avoid its use. Clinical judgment determines the attitude that should be taken toward the risk involved.

Another situation of interest in this perplexing aspect of drug therapy concerns the development of unexpected reactions. Not infrequently a drug is released for interstate commerce after years of laboratory and clinical research and with hope that all pharmacologic properties are known. Then suddenly there appears a report, or several, of, for example, agranulocytosis. Does this mean the drug should be withdrawn from the market? Again the risks and the potential usefulness must be considered. Within the last few days, word has been received of three cases of agranulocytosis following the use of procaine amide, which has been proposed for conditions in which quinidine is effective. One wonders whether this provides sufficient excuse for deletion of the drug from the medical armamentarium or whether it is in the same class as, for example, the sulfonamides and propylthiouracil—too useful for discard but not so free of toxic properties that carelessness can ever be permitted. The evidence at this time seems to support the latter approach.

Physicians today have remarkable tools with which to practice medicine. But, as is true of all tools, improper use is attendant with danger. If there is an unusual risk associated with the use of a drug, but the physician is convinced the drug is necessary for, or at least best suited to, a patient, he should accept the risk as a challenge by which he cautiously approaches his clinical problem. To indict a drug or all drug therapy because occasional reactions are seen is unfair to patients who might benefit therefrom. However, he cannot afford, for his patient's welfare or his own reputation, to use a drug with which he is not familiar or which he believes is too dangerous for his practice. In the final analysis, his decision must rest on his knowledge and experience and on sound judgment.

INTERNATIONAL SANITARY REGULATIONS

On May 25, 1951, the Fourth World Health Assembly unanimously approved the new WHO Sanitary Regulations No. 2. These regulations, which were approved by 64 member-states of the WHO, provide for the first time a single set of rules concerning international traffic. Governments now have nine months in which to make reservations, which may or may not be approved by the Fifth World Health Assembly. The regulations will then go into force in all countries concerned on Oct. 1, 1952. In reality, that will mean all countries other than those of the communist block.

The system of international sanitary regulations has already been tried in connection with the international classification for diseases and causes of death, but mor-

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tality statistics are less controversial and have less economic consequence than international traffic regulations.

It took exactly a century for the national health administrations to arrive at this state of development of international relations. The first international sanitary conference met in Paris in 1851. Like the subsequent international sanitary conferences held during the next 40 years in various capitals, ranging geographically from Constantinople to Washington, it dissolved with no other result than posing the problem and keeping it alive in the minds of the governments. The first real international sanitary convention that came into effect was that of 1893. Attempting to keep abreast with the progress of medical science, other conventions followed, notably the International Sanitary Conventions of 1903, 1905, 1912, and 1926, the Pan American Sanitary Convention of 1905, the Pan American Sanitary Code of 1924, the International Sanitary Convention for Aerial Navigation of 1933, and the Sanitary Conventions of 1944.

Except for the Pan American Sanitary Code, the conventions were ratified only by a limited number of the countries concerned. At present, 13 major sanitary conventions, ranging in time from 1903 to 1946, are in force for various countries while some countries have never signed any conventions, thus adding greatly to the confusion of all sanitary measures that can be taken in regard to international traffic. All these conventions, with the exception of the Articles of the Pan American Sanitary Code referring to subjects other than the pestilential diseases, will now be superseded by the new WHO regulations.

The first draft of the regulations was prepared by the WHO Expert Committee on Epidemiology and Quarantine. This draft was sent to all governments for comment. The comments were, as far as possible, embodied in the new draft, which was then submitted to the special committee constituted by the Third World Health Assembly. This committee met in Geneva from April 9 to May 5, 1951. There were official delegations from 34 countries at the session.

The Fourth World Health Assembly meeting in Geneva, on May 7, 1951, reconstituted the committee as a committee of that Assembly, thus enabling all the 64 governments represented at the Assembly to participate in the deliberations. Last-hour changes were made to satisfy those who had previously been absent, and on May 25 the regulations were approved by the Assembly without dissent.

The new regulations recognize that complete protection against the introduction of pestilential diseases depends on the eradication of the existing foyers. Until such eradication is achieved, there is a continuing danger of their spread. The regulations define maximum measures that may be applied when necessary and are in general less restrictive on international traffic than the former conventions. It is expected that greater security against the spread of infection will be attained with fewer restrictions on international traffic.

One fundamental principle of the regulations which was successfully promoted by the American delegation was that complete information regarding the occurrence of any case of a pestilential disease must be promptly available from all parts of the world. The duty of reporting has, therefore, been extended, and the WHO Epidemiological Intelligence has been greatly strengthened. At present, many restrictive quarantine measures are solely due to the lack of immediate and reliable information regarding the occurrence of smallpox and murine plague.

The American delegation also insisted that proper machinery should be set up for current review of the functioning of the regulations. Such reviews have not hitherto been available, nor has there been any competent authority for analyzing the information available. An appropriate committee to be set up for this purpose within the WHO should make it possible from time to time to review the regulations in the light of acquired experience. Unnecessary restrictions might thus be removed, and measures which have been found lacking might be added to the regulations. The present regulations refer mainly to plague, cholera, yellow fever, smallpox, typhus, and relapsing fever. The Assembly, therefore, decided to set up an appropriate committee to consider additional regulations which may be necessary in regard to other diseases. Among the problems yet to be solved is the prevention of international transport of malaria vectors. The importance of such control will rapidly increase with the extent of the areas liberated from malaria vectors.

The regulations contain provisions regarding the establishment of direct transit areas in airports for accommodating, in segregation, the passengers and crew, thus breaking their voyage without their leaving the airport. It is expected that this measure will do away with many of the hindrances to rapid travel by air when the voyage extends over a number of countries. Radio pratique has been introduced for the first time in the international agreements for ships and aircraft, which may thus avoid delay by reporting on their sanitary state before arrival.

Measures against plague have definitely been centered on the control of rodents rather than on the human cases. The delineation of yellow fever endemic zones has been radically changed. At present, measures are taken against very large areas in Africa and South America where the virus exists or is known to have existed among jungle animals with no, or only incidental, human cases. Under the new regulations, the presence of Aedes aegypti also is required before a locality can be included in the endemic zone. It was the belief of the majority of the committee that only the presence of an efficient domestic vector, such as the Aedes aegypti, would make it practically possible to spread the disease beyond national frontiers. This provision will greatly reduce the South American yellow fever endemic zone and consequently facilitate aerial traffic in that part of the world.

The chapter concerning smallpox was completely rewritten. The proposal of the American delegation that any person on an international journey may be required to possess a valid smallpox certificate was adopted. So long as smallpox infection exists in so many countries and information is not always readily available regarding its occurrence, it is believed that this measure is necessary in order to limit international spread. The smallpox certificate was simplified, on the other hand, so that travelers will not have to wait for the reading of the

results of the vaccination. It is generally recognized that most of the readings of revaccinations made in various parts of the world are of slight value. Instead, it must be stated on the certificate whether a successful primary vaccination or a revaccination is in question.

Several articles on measures against typhus were deleted, as they were considered unnecessary in view of the simple methods of control with dichlorodiphenyltrichloroethane (DDT) now available. No ship or aircraft will be delayed on account of a case of typhus or relapsing fever on board.

Bills of health are abolished. Maritime declarations of health, deratting or deratting exemption certificates and vaccination certificates against yellow fever, cholera, and smallpox are the only international documents that may be required. Typhus, plague, or other vaccinations may not be required as a condition of entry into a territory. The sanitary declaration of an aircraft will be part of the general declaration. The proposal of the American delegation to the effect that a vaccination certificate issued to an active member of the armed forces shall be accepted in lieu of an international certificate was adopted. The period of validity of the yellow fever certificate was extended to six years. The new smallpox vaccination certificate may be used from Dec. 1, 1951, for any state which within three months of the adoption of the regulations by the Assembly declares that it does not intend to make reservations in that respect.

Today, Southeast Asia lives in deadly fear of the introduction of yellow fever. The Near East dreads cholera, and the United States fears smallpox. None is protected as it ought to be against these dangers. Each part of the world has its own problems. Nevertheless, on May 25, 1951, by mutual concessions, 64 free countries agreed on a common text for solving their quarantine problems, and a United Nations specialized agency was appointed executive of the agreement.

TRENDS IN CANCER MORTALITY

The Metropolitan Life Insurance Company has recently compared the mortality rates from malignant neoplasms during the periods 1946-1947 and 1949-1950.[1] The over-all percentage change in death rate for white policy holders between one and 74 years of age was an increase of 4% for the males and a reduction of 3% in females. The reduction in females occurred chiefly at ages 25 to 74, with only slight changes at ages one to 24 years. In the males, there was a decline in mortality at ages one to 14 years and 45 to 74, a small increase at 15 to 24, and an appreciable increase at 24 to 44. Both sexes show a decline in mortality for cancer in accessible sites, reduction being particularly marked for cancer of the uterus in females and cancer of the buccal cavity in males. For cancer in inaccessible sites, the mortality rate declined slightly between 1946-1947 and 1949-1950 in females but increased in males. Cancer of the respiratory tract and of the pharynx taken together increased 30.4% for males and 10.3% for females, the increases being attributable to some extent to improved diagnostic techniques, increasing alertness of the physician, and use of mass x-ray examinations. Both sexes showed an increase in death rate for cancer of the pancreas, while the death rate for cancer of the ovary and other female genital organs increased by about one-sixth. In both sexes, however, there was a reduction in mortality from cancer in a number of inaccessible sites, including the stomach, intestines and duodenum, rectum and anus, liver and biliary passages, and bladder. The death rate from leukemia increased markedly in both sexes, possibly a reflection of improved diagnosis. While the success of the campaign for early recognition and treatment of cancer cannot be judged solely by this report, the reductions in mortality for many sites of cancer are encouraging.

1. The Postwar Cancer Record, Statistical Bulletin, Metropolitan Life Insurance Company **32**: 8 (May) 1951.

MALPRACTICE AND THE PHYSICIAN

Elsewhere in this issue of THE JOURNAL (page 54) appears a special report of the Committee on Medicolegal Problems dealing with malpractice claims. The report emphasizes the preventive aspects of the problem and contains many suggestions as to what can be done to reduce the incidence of unjust suits. Committees have been created by many state and local medical associations to study the malpractice problem and to assist patients and physicians in adjusting differences that may arise, some of which may be forerunners of litigation. Such committees will find this report of significant value, as will also individual physicians. Patients who have just grievances should be aided in obtaining proper and prompt adjustments, but many claims, as the report points out, result from a misunderstanding of the legal responsibilities involved in the physician-patient relationship. The report should serve to clarify an appreciation of these responsibilities. Reprints will be made available by the Committee on Medicolegal Problems.

SUBLINGUAL ABSORPTION OF HEPARIN

The success of heparin in the treatment of frostbite [1] and the value of initiating such treatment in the field before hospitalization of soldiers led Litwins [2] and associates of Beth Israel Hospital, New York City, to test the possibility of sublingual administration of this drug. Wafers containing 125 mg. of sodium heparin were placed in the sublingual pouch of 10 volunteers, where they rapidly disintegrated. Absorption was usually complete in 10 minutes. Periodic determinations of the blood coagulation time showed that in most instances a therapeutically effective prolongation was attained one-half hour after administration of the heparin and maintained for some four hours. The New York clinicians believe from their data that sublingual administration of heparin may in time be recognized as a method of choice for the anticoagulant treatment of myocardial infarction, pulmonary embolism, and thrombophlebitis, and in vascular surgery.

1. Lang, K.; Boyd, L. J., and Loewe, L.: The Functional Pathology of Frostbite and the Prevention of Gangrene in Experimental Animals and Humans, Science **102**: 151 (Aug. 10) 1945.

2. Litwins, J.; Vorzimer, J. J.; Sussman, L. N.; Applezweig, N., and Etess, A. D.: Sublingual Administration of Heparin, Proc. Soc. Exper. Biol. & Med. **77**: 325 (June) 1951.

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MEDICAL NEWS

CALIFORNIA

Facilities for the Chronically Ill.—San Francisco's Chronic Illness Service Center, organized in 1950, is now on a full-time working basis and will assist San Francisco Medical Society members who may have problems among their patients with chronic illness. The city is reported to be one of five in the nation which has developed its own Chronic Illness Service Center.

COLORADO

Narcotic Violation.—Dr. George A. Glenn, Denver, pleaded *nolo contendere* to all counts in the indictment charging violation of the federal narcotic law. On July 11 he was sentenced to serve one year and one day on five counts to run concurrently, and on the sixth count sentence was suspended and he was placed on probation for two years, the probation to begin at the expiration of the sentence on the first five counts.

GEORGIA

University News.—Dr. Alvin G. Foraker and Dr. Abner Golden have been promoted from assistant professors to associate professors of pathology at the Emory University School of Medicine, Atlanta. Other promotions include Dr. Philip Bondy from associate in medicine to assistant professor of medicine, and Dr. James F. Olley from associate in pathology to assistant professor of pathology.

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ILLINOIS

Hospital News.—Last spring, with appropriate ceremonies ground was broken for the new Memorial Hospital in Marion. The new 50-bed hospital will cost about $900,000.

Drive on Unlicensed Healers.—According to the *Chicago Daily News*, C. Hobart Engle, new director of the Illinois Department of Registration and Education, has asked all state's attorneys to "crack down" on more than 400 unlicensed healers in Illinois. About 100 of these are in the Chicago area. The unlicensed practitioners include chiropractors, naprapaths, and naturopaths. Each prosecutor has been given a list of unlicensed healers in his county, according to Jack L. Sheer, chief attorney for the department.

Chicago

Lectures on Biophysical Aspects of Virology.—A series of lectures and demonstrations in the biophysical aspects of virology will be given Sept. 20-22 by Dr. Max A. Lauffer, professor of biophysical chemistry, University of Pittsburgh. These lectures are part of the Gehrmann lecture series sponsored by the department of bacteriology of the University of Illinois College of Medicine. The following program of lectures will be given at 1 p. m. each day, followed by a demonstration at 3 p. m. unless otherwise indicated:

Sept. 20, Ultracentrifugation, at Abbott Hall, University of Chicago; the use of centrifugation for preparation and characterization of viruses.

Sept. 21, Electrophoresis, at the North Amphitheatre, Presbyterian Hospital; the use of electrophoresis for purification and characterization of viruses.

Sept. 22, Electron Microscopy, 9:30 a. m. at University of Illinois Research and Educational Hospitals; the use of electron microscopy in the study of viruses, 11 a. m., Room 342, University of Illinois Dental-Medical-Pharmacy Building.

All interested are invited to attend the lectures, but there will be room for only 20 at the demonstrations. All who wish to attend may register by writing to Dr. J. E. Kempf, Department of Bacteriology, University of Illinois, 808 S. Wood St., Chicago 12, before Sept. 15.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education and public health. Programs should be received at least three weeks before the date of meeting.

Grants for Research.—The Hektoen Institute for Medical Research has received the following contributions for research:

For investigations by a team headed by Dr. Hans Popper, an annual contribution of $16,000 was received from the Dr. Jerome D. Solomon Memorial Research Foundation for research in liver diseases; from the Atlas Powder Company, $13,250 for the investigation of the influence of emulsifying agents on fat metabolism; from the Nepera Chemical Company, Inc., $3,500 for the study of toxicologic effects of pharmacologic agents, and from the U. S. Vitamin Corporation, $4,140 for research on the physiological effects of parenteral lipotropic administration. For investigations by a team headed by Dr. Oscar Felsenfeld, $10,000 was received from the Dr. Leonard H. and Louis Weissman Medical Research Foundation for research in virus diseases; from the Commercial Solvents Corporation, $12,000 for study of the inhibition of viruses transferable from animals to man, and $12,000 for studies in mycology and parasitology; and from the Eaton Company, $11,000 for further studies of nitrofurans. For investigations by a team under Dr. Steven O. Schwartz, $5,000 was received from the Olivia Sue Dvore Foundation, $1,800 of which will be used for a research fellow in hematology and the balance for research on leukemia; and from the Edward Friedman Leukemia Fund, $3,000 for the continuation of research on leukemia. For investigations on breast carcinoma by a team headed by Dr. Louis P. River, an annual allocation of $7,500 has been made by the Dr. Jerome D. Solomon Memorial Research Foundation. The Karl A. Meyer Fellowship of the foundation, held by Dr. Hyman S. Lans, has been awarded for another year for research in potassium metabolism in surgical conditions.

INDIANA

Faculty Appointments.—Twenty-six members of the faculty of the Indiana University School of Medicine, Indianapolis, have been advanced in academic rank by the board of trustees. The promotions included the conferring of the title of professor emeritus in proctology on Dr. Joseph W. Ricketts; professor emeritus in genitourinary surgery on Dr. Arthur F. Weyerbacher and Dr. Homer G. Hamer, and associate professor emeritus in pediatrics on Dr. J. Don Miller. Advanced to fill vacancies in departmental chairmanships were Dr. Marlow W. Manion, named professor of otolaryngology and chairman of the department of otorhinolaryngology and broncho-esophagology, and Dr. Lyman T. Meiks, named chairman of the department of pediatrics and professor of pediatrics. Dr. Manion, a member of the staff for 21 years, succeeds Dr. Carl H. McCaskey, who retired a year ago after 29 years on the faculty. Dr. Meiks succeeds Dr. Matthew Winters as chairman of the department of pediatrics, a post which Dr. Winters had filled with distinction for 20 years. Dr. Meiks has been a member of the medical school staff since 1931 and has served as full-time pediatrician at the James Whitcomb Riley Hospital for Children. Dr. Edward B. Smith, St. Louis, has been appointed professor of pathology. He served for two years as an instructor in pathology at Washington University, St. Louis, before entering the Army Medical Corps in 1942. After leaving the army in 1946 Dr. Smith was on the pathology staffs of the University of Pennsylvania, Philadelphia, and Baylor University, Houston.

IOWA

Dr Gilman Wins Chemistry Award.—Henry Gilman, Ph.D., professor of chemistry at Iowa State College of Agriculture and Mechanical Arts at Ames, has won the 1951 Iowa Award, given by the Iowa Section of the American Chemical Society for meritorious work in research, teaching, or industry. The medal will be presented to Dr. Gilman at a dinner in Iowa City on Dec. 7. In addition to war research on antimalarials, Dr. Gilman has done work on the relationship between the physiological action and the chemical constitution of local anesthetics, antibiotics, hypnotics, and analgesics.

KANSAS

Public Health Appointments.—Dr. Thomas R. Hood, formerly director of the Topeka-Shawnie County Health Department, was appointed executive secretary of the Kansas State Board of Health, effective Aug. 1. Dr. Robert H. Riedel, who had accepted a temporary appointment to this position, has returned to his regular work as director of the Division of Cancer Control. Dr. Floyd C. Beelman, former executive secretary, resigned in May to take up defense work in Washington, D. C. Dr. H. R. Wagenblast of the Wichita-Sedgwick County Health Department, is the new director of the Lawrence-Douglas County Health Department in Lawrence.

Teacher Training Program for the Deaf.—September 4 will initiate a new one-year teacher training program for the deaf at the University of Kansas Medical Center, Kansas City. Although the state has had some type of school for the deaf since 1861, it has been necessary to hire teachers trained in one of the 19 other schools in the country offering certified training programs for teachers of the deaf. At present, only about one-fourth of the hard-of-hearing children in Kansas are being helped in any way. A recent survey of school children in Leavenworth, initiated by Dr. LaVerne B. Spake, Kansas City, showed almost 6% were hard-of-hearing. This means that in the state of Kansas 28,197 children are probably hard-of-hearing. Lack of teachers has prevented any expansion of aid to them. The new teacher training program will utilize the combined facilities and members of the faculties of the university's school of education, the Kansas School for the Deaf at Olathe, and the hearing and speech department of the medical center. Entrance requirement is a bachelor's degree in education. At the conclusion of the course registrants will receive a master's degree in education. They will also be eligible for certification by the Conference of Executives of American Schools for the Deaf.

LOUISIANA

Dr. Kilbourne to Direct Division.—Dr. Edwin D. Kilbourne, New York, has been appointed associate professor of medicine and director of the division of infectious disease at Tulane University of Louisiana School of Medicine in New Orleans. He comes to Tulane from the hospital of the Rockefeller Institute for Medical Research, where he was assistant physician. The division of infectious disease plans to build up basic research in the department, with emphasis on virus diseases.

MISSOURI

Postgraduate Course for General Practitioners.—The St. Louis Academy of General Practice in cooperation with Washington University will hold its second postgraduate course for general practitioners beginning Sept. 18. The course consists of lectures from 8 to 10 a. m., Tuesday and Thursday, for six weeks. It affords 24 hours of formal postgraduate study, accredited by the Committee on Education of the American Academy. Over one hundred general practitioners are now registered.

NEW YORK

Society News.—Dr. Samuel W. Moore, New York, will speak on "Pathology and Complications of Acute Cholecystitis" before the Jefferson County Medical Society at 6:30 p. m. Sept. 18 at the Black River Valley Club in Watertown.

Hospital News.—St. James Mercy Hospital, Hornell, on July 15 opened its new million dollar wing which was begun in the fall of 1949. The hospital now has a 145-bed capacity and such new departments as a postoperative recovery room, a complete cystoscopy department, and a completely new surgical department that includes three major operating rooms and an eye, ear, nose, and throat operating room.

State Hospitals Appointments.—Dr. Francis J. O'Neill has been appointed senior director of Central Islip State Hospital and Dr. Bascom B. Young, director of Utica State Hospital, effective Aug. 1. Dr. O'Neill's appointment is a promotion from his position as director of Utica State Hospital. Dr. Young, present assistant commissioner of mental hygiene, will assume the directorship left vacant by Dr. O'Neill's transfer.

New York City

First Harvey Lecture.—Dr. A. R. Todd, professor of chemistry, University Chemical Laboratory, Cambridge, England, will deliver the first Harvey Lecture of the current series at the New York Academy of Medicine on September 27 on "The Nucleotides: Recent Chemical Research and Its Biological Implications."

Two-Year Course in Psychotherapy.—The Group Psychotherapy Institute will now offer, in addition to seminars, a two-year consecutive course that will include one year of preliminary training and one year in group psychotherapy. The courses will be offered for five hours a week for 30 weeks of each year, and the time of day will be arranged to suit the participants. The number of students will be limited to 20, and preference will be given to psychiatrists, psychiatric caseworkers, and clinical psychologists engaged in individual or group psychotherapy, especially in an agency or hospital setting. The tuition is $150 per year. For information write to Group Psychotherapy Institute, Inc., 105 E. 22 St., New York 10.

Efficiency Study for Municipal Hospitals.—The Hospital Council of Greater New York, at the request of the department of hospitals, is undertaking a study of the types of patients and the different facilities and programs available for acute, chronic, and convalescent cases in municipal hospitals. The study, made possible through a grant from the New York Foundation, is to be completed early next year. Dr. Marcus D. Kogel, hospital commissioner, said that the Board of Hospitals believes that more effective planning for the future of hospitals of the department could be made after pertinent information was available concerning types of patients and the factors that influence prolonged hospital stay. It is also planned to analyze the services required by patients currently under care to determine the facilities and services which should be provided. The hospital council will evaluate the relative cost of providing hospital care for acute and chronic illness in patients. Outpatient services will also be studied in their relation to more effective use of convalescent institutions.

Graduate Fortnight.—The New York Academy of Medicine in cooperation with the New York Heart Association will present its 24th Graduate Fortnight Oct. 8-19 on "Disorders of the Circulatory System." Evening sessions beginning at 8:30 p. m. in the New York Academy of Medicine will be addressed by the following guest speakers:

Herrman L. Blumgart, Boston, Coronary Disease: Clinical Pathologic Correlations and Physiology.
John W. Gofman, Berkeley, Calif., Diet and Lipotropic Agents in Atherosclerosis.
Albert Szent-Gyorgyi, Woods Hole, Mass., Contraction in Heart Muscle.
Lewis Dexter, Boston, Dynamics of Acquired Valve Lesions.
Eugene A. Stead Jr., Durham, N. C., Edema and Dyspnea of Heart Failure.
Louis N. Katz, Chicago, Importance of Cardiac Arrhythmias.
Irvine H. Page, Cleveland, Renal and Vasomotor Factors in Hypertension.
Merrill C. Sosman, Boston, Roentgen Diagnosis in Cardiovascular Disease.
Thomas H. Hunter, St. Louis, Treatment of Bacterial Diseases of the Heart and Pericardium.

Morning panel discussions will be held at the academy on Oct. 9, 12, 16, and 19. There will be hospital clinics each day from 2 to 5 p. m. Registration fee for those not members of the academy is $10.

NORTH CAROLINA

Dr. Sawyer Goes to California.—Charles H. Sawyer, Ph.D., professor of anatomy at The Duke University Medical School, Durham, and a member of the faculty since 1944, this fall will become professor of anatomy at the new University of California at Los Angeles School of Medicine. Before joining the Duke staff, Dr. Sawyer had taught at Yale and Stanford universities.

Dr. Burnett to Head Department of Medicine.—Dr. Charles Hoyt Burnett, professor and chairman of the department of internal medicine, Southwestern Medical School of the University of Texas, Dallas, becomes professor and head of the

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department of medicine at the University of North Carolina, in Chapel Hill in September. Other new appointments to the staff of the school of medicine include the following: Dr. William J. Cromartie as associate professor of bacteriology and director of the bacteriological laboratory in University Hospital; Dr. Charles B. Taylor as associate professor of pathology; Basil L. Truscott, Ph.D., as assistant professor of anatomy, and Drs. Clarence M. Miller Jr. and James B. Caulfield as fellows in pathology.

Training Center for Premature Infant Care.—The Duke University will become North Carolina's first training center for premature infant care this fall. Public health nurses and graduate nurses in hospitals throughout the state will be trained in caring for premature babies at the Duke School of Nursing. The North Carolina Premature Care Program, administered by the State Board of Health through the pediatric consultant, Dr. Robert J. Murphy, is sponsored by the North Carolina Pediatric Society. For two and one-half years the state program has sponsored six service treatment centers in North Carolina hospitals but has had no facilities for training nurses. The plan may be expanded for training physicians later on. Deaths in the six hospital service centers have been cut in half since the program was begun two and one-half years ago, spokesmen said. Service centers are located at Duke and Watts hospitals, Durham; Rex Hospital, Raleigh; North Carolina Baptist Hospital, Winston-Salem; James Walker Memorial Hospital, Wilmington, and Victoria Hospital, Asheville. There are now more than 8,000 premature infants born in North Carolina every year, and about 4,000 need care at special hospital centers.

OREGON

Constitutional Make-Up and Disease.—The University of Oregon Medical School, through a grant of $100,000 from the Rockefeller Foundation, New York, will participate in an intensive study of the relation between physical make-up and disease. The study will be organized by Dr. William H. Sheldon of Columbia University College of Physicians and Surgeons and the head of the college's constitutional laboratory. Dr. Sheldon is said to expect it will take two generations to complete the study. In establishing physical categories he and his co-workers and assistants have photographed more than 100,000 persons. Members of the department of medicine of the medical school will cooperate.

PENNSYLVANIA

Regional Meeting of Pathologists.—The Pennsylvania Association of Clinical Pathologists, the Clinical Pathological Society of Pittsburgh, and the Middle-Eastern Regional Committee of the College of American Pathologists will meet at the Roosevelt Hotel in Pittsburgh Sept. 14-15. A slide seminar on "The Pathologic Anatomy of Virus Diseases" opens the morning session Sept. 14. Slide sets can be reserved by registrants who pay the slide seminar registration fee of $5, which should be forwarded to Dr. Elwyn L. Heller, Department of Pathology, University of Pittsburgh, Pittsburgh 13. The seminar will be moderated by Dr. Heller, and Dr. John P. Wyatt, professor of pathology, St. Louis University School of Medicine, will serve as referee. A social hour and informal dinner are scheduled for Friday and Saturday evening at the Roosevelt Hotel. There will be a business meeting of the Pennsylvania Association of Clinical Pathologists Sept. 16.

Philadelphia

Personal.—Dr. Archer P. Crosley Jr., assistant instructor of medicine at the University of Pennsylvania School of Medicine, has been appointed a staff physician in the medical division of Sharp & Dohme, Inc.

Gift for Televising Operations.—A gift of $30,000 for the purchase of equipment to be used in the color televising of surgical operations performed in the Hospital of the University of Pennsylvania, Philadelphia, has been announced. The gift is from anonymous donors and friends of Dr. Isidor S. Ravdin, John Rhea Barton Professor of Surgery in the University of Pennsylvania School of Medicine and chairman of the Harrison Department of Surgical Research.

Pittsburgh

Dr. Wishik Joins University Staff.—Dr. Samuel M. Wishik, New York, has been appointed professor of maternal and child health at the University of Pittsburgh School of Public Health, where he and his staff will develop a program of teaching and research. Emphasis will be given to public health administration. Dr. Wishik's most recent position has been that of director of child health in New York City; formerly he was chief of the program planning section of the United States Children's Bureau, and director of maternal and child health and crippled children for the Territory of Hawaii. He served in the United States Public Health Service during the war. His past teaching activities include appointments at New York Medical College, Columbia University, The Johns Hopkins University, and the University of Hawaii.

SOUTH DAKOTA

University Appointments.—Five new appointments have been made to the resident teaching staff of the University of South Dakota School of Medicine, Vermillion. Charles D. Cox, Ph.D., of Pennsylvania State College, will be professor and chairman of the department of microbiology and public health. He has taught in the Medical College of Virginia in addition to Penn State. During the war he was in charge of bacteriology for the China-Burma-India theater medical laboratory. Dr. Amos C. Michael will come to the university on Dec. 15 as associate professor of pathology. He has held the same position at Indiana University, Indianapolis. Dr. Louis F. Michalek is already on duty as assistant professor of pharmacology in the school of medicine. Adaline N. Mather, Ph.D., has been appointed assistant professor of microbiology, beginning Sept. 1; she has been at Southern Illinois University in the department of bacteriology. Robert Trankle, M.A., started his work July 1 as instructor in microbiology. Dr. Warren L. Jones, Sioux Falls, has been appointed associate in clinical physiology; Dr. Robert S. Monk Jr., Yankton, instructor in clinical anatomy, and Dr. Frederick M. Stark, Sioux City, Iowa, clinical assistant professor of neurology and psychiatry.

TENNESSEE

Cancer Research Laboratory.—The University of Tennessee Medical Unit's Cancer Research Laboratory has been added to the medical center in Memphis. Funds for the building, completed at a cost of $499,088, were made available by the National Cancer Institute of the United States Public Health Service.

General Practice Clinic.—Dr. Paul S. Williamson, general practitioner of Vernal, Utah, will be the director of the new Family General Practice Clinic to be established by the University of Tennessee College of Medicine in the outpatient department of John Gaston Hospital in Memphis, and opened Sept. 27. The clinic marks a departure from the trend to specialization in medicine. It will stress for graduating medical students the idea of "family" practice. Tennessee is in need of family practitioners. Dr. Williamson has been engaged in general practice at Vernal since 1947. The clinic will be operated under the division of preventive medicine.

TEXAS

New Laboratory.—A tissue metabolism research laboratory has been established at the University of Texas Medical Branch, Galveston, under the direction of Wiktor W. Nowinski, Ph.D., associate professor of neurochemistry. The laboratory will be devoted to clinical research concerned with tissue metabolism in the treatment of burns, and in the promotion of repair and regeneration.

Reprint on Yellow Fever Epidemics.—The University of Texas Press is arranging for the publication of a reprint of Dr. Ashbel Smith's account of the yellow fever epidemic in Galveston in 1839. The reprint is being prepared with a biographical sketch of Dr. Smith and a general account of the development of knowledge regarding the control of yellow fever. Dr. Smith

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(1805-1886) was a founder of the University of Texas and first chairman of the board of regents. He had previously served as dean of the Texas Medical College in Galveston, which preceded the University of Texas Medical Branch.

VIRGINIA

Society Honors Managing Editor.—The August issue of the *Virginia Medical Monthly*, by order of the council of the Medical Society of Virginia, is dedicated to Miss Agnes V. Edwards and her father, both of whom have been and were long associated with the publication. Dr. Landon B. Edwards started the monthly as a private enterprise in 1874, passed it to his son, Dr. Charles M. Edwards, on his death in 1910, and when the latter went to war Miss Edwards took over and has managed it since that time. In 1924 she was officially elected business manager and executive secretary of the Medical Society of Virginia, which had purchased the journal in the fall of 1919. The medical society dedicated the August issue to her as an expression of appreciation for her work.

WEST VIRGINIA

Board Elections.—Dr. William M. Jarrett, Charleston dentist, was re-elected chairman of the state board of health at the meeting held in Charleston June 29. He will serve for an additional two years. Dr. Walter E. Vest of Huntington was re-elected chairman of the Medical Licensing Board for a two-year term. He was the first chairman of the board, organized July 1, 1949. He had previously served for 12 years as president of the old public health council, which was replaced by the licensing board. The fall meeting of the Medical Licensing Board will be held at the Capitol in Charleston, Oct. 1-3, for the purpose of examining applicants for licensure to practice in West Virginia.

Medical Press-Radio Code.—The Doctor-Press-Radio Code of Ethics, prepared by a committee composed of Dr. E. Lyle Gage, Bluefield, representing the West Virginia State Medical Association, and Francis P. Fisher and George Clinton of Parkersburg, representing, respectively, the State Newspaper Council and the State Broadcasters' Associati n, was formally adopted by the State Newspaper Council at a meeting at Spencer July 27. The code had the unanimous approval of representatives of the press, radio, and medical profession who attended the annual press-radio conference sponsored by the state medical association, held at Charleston Jan. 28. It had been approved previously by the council of the state medical association, and it was approved by the West Virginia Broadcasters' Association at a meeting held last spring.

WISCONSIN

Funds for Cancer Research.—The University of Wisconsin regents have accepted a grant of $45,000 for cancer research from the estate of the late Mrs. Mary E. Stewart, former Wausau resident. Mrs. Stewart, daughter of the late Alexander Stewart, who was a pioneer lumberman in the Wausau area, willed her estate of nearly $5 million to her sister, with the provision that after the sister's death the money was to be used for cancer research. The sister has released the funds for current use in cancer research. McArdle Memorial Laboratory, university cancer research center, already has benefited from the Stewart estate by grants of $30,000 in December, 1949, and $15,000 in July, 1950. The present $45,000 grant is now available for use. The money is used to pay the salaries of some of the younger key staff people and to purchase supplies and apparatus.

WYOMING

Blood Typing and RH Testing Program.—In response to requests by Wyoming physicians, and as an addition to the Division of Maternal and Child Health Services, the state board of health at a recent meeting approved the initiation of a state-wide program for the routine blood typing and Rh testing of all prenatal blood specimens sent to the Wyoming Public Health Laboratory in Cheyenne. This program began August 1. The laboratory has been performing Rh tests on blood specimens sent in special containers, but has not done blood typing. The new Rh and blood typing program will require only a single clotted blood specimen for an Rh test, blood typing, and prenatal serologic test for syphilis. As planned this new service will be limited strictly to obstetrical cases, except that Rh tests will be performed on husbands of Rh-negative women on special request.

GENERAL

Survey of County Chronic Diseases Programs.—In a recent survey of activities of 757 county medical societies, the following programs related to chronic diseases were reported:

Five hundred and forty-five county medical societies participate in tuberculosis control programs, and 533 in cancer control programs; and 367 cooperate in a diabetes control program, and 149 in a rheumatic fever control program. Seventy-six county medical societies reported that they are experimenting with multiphasic screening. The survey was made by the Council on Medical Service of the American Medical Association.

Alcohol Committee Enlarges Scope.—The National Committee on Alcohol Hygiene, Inc., with national headquarters in Baltimore, has enlarged its scope of education to include the expanding American social ills of today. Besides educational reports on alcoholism and alcoholics, the committee will disseminate scientific articles for the laity on dope and drug addiction, crime and criminality, and psychological sexual illnesses and divorce. The first report, now available for distribution, is titled "How to Help an Alcoholic." The second report will be issued also in booklet form in September entitled "The Dope on Dope." The executive director of the committee is Dr. Robert V. Seliger, Baltimore.

Dr. Hartley to Edit Northwest Medicine.—Dr. Herbert L. Hartley, Seattle, has been named editor-in-chief of *Northwest Medicine*, succeeding Dr. Clarence A. Smith. Dr. Smith, who helped to found the medical journal in 1901 and who observed his 90th birthday anniversary in January, was named editor emeritus. The journal is the official publication of the state medical associations of Washington, Oregon, Idaho, and Alaska. Dr. Hartley, who has practiced in Seattle for 19 years, was graduated from the University of Iowa Medical School in 1928. He served in the Navy Medical Corps for four years during World War II. The new editor is a member of the publication committee of *GP*, the journal of the American Academy of General Practice.

The Cardiac in Industry.—The Joint Committee on the Cardiac-in-Industry has held its first meeting in New York to consider problems of education, research, rehabilitation, and employability of workers with heart disease. The committee was set up by the American Heart Association. Its chairman is Dr. Leonard J. Goldwater, professor of industrial hygiene, Columbia University School of Public Health, New York. Other members are Drs. Rufus B. Crain, medical director, Eastman Kodak Company, Rochester, N. Y.; Edward M. Kline, medical consultant, General Electric Company, Cleveland; Leo Price, director, Union Health Center, International Ladies' Garment Workers' Union, New York; Brandt F. Steele, internist and psychiatrist, Philadelphia, and James V. Warren, physiologist, Emory University School of Medicine, Atlanta.

Markle Scholar Nominations.—The John and Mary R. Markle Foundation invites deans of medical schools in the United States and Canada to make nominations for the fifth group of Scholars in Medical Science on or before Dec. 1, 1951. Each school may nominate one candidate. Candidates should have completed the usual fellowship training in some area of science related to medicine and should hold, or expect to hold, in the academic year 1952-53 a full-time faculty appointment on the staff of a medical school. The grants are not intended for support of interns or residents, or for those considered by the faculty as advanced students still in training. Grants of $30,000, payable at the rate of $6,000 annually, will be made to the schools over a five-year period toward the support of each scholar and his research. The number of scholars to be appointed in 1952 has not yet been determined. Twenty were named in 1950 and in 1951. A new booklet about the plan, with suggestions for making nominations, is available on request from the foundation, 14 Wall St., New York 5.

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Obstetric Seminar.—This seminar, annually sponsored by the Medical College of Georgia and the bureaus of maternal and child health of the South Carolina, Georgia, and Florida state health departments, will be held at the Sheraton Plaza Hotel, Daytona Beach, Fla., Sept. 10-12. The meeting is approved for credit hours by the American Academy of General Practice. Visiting lecturers include Dr. R. Gordon Douglas, professor of obstetrics, Cornell Medical School, New York; Dr. Edith L. Potter, associate professor of pathology, University of Chicago; Dr. Francis B. Carter, professor of obstetrics, The Duke University, Durham, N. C.; Dr. Carl Huber, professor of obstetrics and gynecology, Indiana University, Indianapolis; Dr. Fred L. Adair, Mary Campu Ryerson emeritus professor of obstetrics and gynecology, University of Chicago, and Dr. Charles C. Chapple, associate professor of pediatrics, Hospital of the University of Pennsylvania, Philadelphia. There is no registration fee. Programs are available on request at the Georgia Department of Public Health.

Annual Meeting on Gastroenterology.—The National Gastroenterological Association will hold its meeting at the Drake Hotel in Chicago Sept. 17-19. The program will include a symposium on peptic ulcer, in which Dr. Andrew C. Ivy, Chicago, will present the physiological aspects; Dr. David J. Sandweiss of Detroit, the medical aspects, and Dr. Lester R. Dragstedt of Chicago, the surgical aspects. There will also be symposia on the pancreas, psychosomatic medicine, and carcinoma and other individual papers. Other speakers include Drs. C. Wilmer Wirts and Garfield G. Duncan, Philadelphia; Dr. Charles P. Rhoads, New York; Dr. R. Russell Best, Omaha; Drs. Sidney A. Portis and Walter L. Palmer, Chicago, and Dr. Fred J. Hodges, Ann Arbor, Mich. Immediately following the convention, from Sept. 20 to 22, the association will conduct a course in postgraduate gastroenterology at the Drake under the direction of Drs. Owen H. Wangensteen, Minneapolis, and Isadore Snapper, New York. Further information may be obtained by writing to the Secretary, National Gastroenterological Association, 1819 Broadway, New York 23.

Chest Physicians Essay Award.—The Board of Regents of the American College of Chest Physicians offers a cash prize award of $250 to be given annually for the best original contribution, preferably by a young investigator, on any phase relating to chest disease. The prize is open to contestants of other countries as well as those residing in the United States. The award, together with a certificate of merit, will be made at the annual meeting of the college. Second and third prize certificates will also be given. All manuscripts submitted become the property of the American College of Chest Physicians and will be referred for consideration to the editorial board of the college journal, *Diseases of the Chest*. The college reserves the right to invite the winner to present his contribution at the annual meeting. Five copies of the manuscript, typewritten in English, should be submitted to the executive office, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, not later than April 1, 1952. The only means of identification of the author or authors should be a motto or other device on the title page, and a sealed envelope bearing the same motto on the outside, enclosing the name of the author or authors.

Vitamin Foundation Grants Awarded.—Nine new grants for research in nutrition have been awarded by the National Vitamin Foundation, which makes grants for research semiannually. Among the grants were the following: Max K. Horwitt, Ph.D., State Hospital, Elgin, Ill., was awarded $5,000 for the continuation of studies of nicotinic acid (niacin) deficiency in man and of the possible interrelationships between nicotinic acid, tryptophan, and riboflavin. Nevin S. Scrimshaw, Ph.D., Rochester, N. Y., director of the division of nutrition for the Pan-American Sanitary Bureau, was awarded $8,000 for the continuation of studies on the effectiveness of vegetable protein supplemented by synthetic vitamin B_{12} on the growth and development of undernourished children. Drs. Robert W. Heinle and David R. Weir, Western Reserve University, Cleveland, were awarded $6,000 for the continuation of studies on the hematopoietic role of vitamins of the B group in normal and pathological conditions of animals and human beings. Earle W. McHenry, Ph.D., University of Toronto, Canada, was awarded $9,600 for the study of the relation of vitamin B_6 (pyridoxine) to protein metabolism. Dr. C. Lockard Conley, Johns Hopkins University, Baltimore, was awarded $5,000 for the study of the absorption, utilization, and excretion of vitamin B_{12}.

Catastrophic Accidents.—Disasters in which the list of dead tallied 100 or more occurred 13 times in the United States during the 1941-1950 decade, Metropolitan Life Insurance Company statisticians report. The highest toll was wrought by the Texas City fire and explosion of April, 1947, in which 561 lives were lost. Next highest in number of deaths were the 1942 night club fire in Boston, killing 492, and the explosion of two ammunition ships at Port Chicago, California, in 1944, which cost 322 lives. The other ten disasters in which 100 or more died are the following:

	Dead
Hartford, Conn., circus fire, 1944	168
Texas and Oklahoma tornado, 1947	167
Pennsylvania, West Virginia, and Maryland tornado, 1944	159
Cleveland, Ohio, gas tank explosion, 1944	130
Oklahoma, Missouri, and Arkansas tornado, 1945	119
Atlanta, Ga., hotel fire, 1946	119
Southern and Midwestern States tornadoes, 1942	111
Centralia, Ill., coal mine explosion, 1947	111
New York Bay, N. Y., destroyer explosion, 1944	100
Northeastern United States, wind and snow storm, 1950	100

From a continuing study of accidents in which five or more lives are lost, the statisticians note that there have been more such accidents during the post-war years than during the war years, but the number of deaths has been lower. From 1941 to 1945 there were 482 catastrophes costing 6,801 lives, but from 1946 to 1950 there were 568 such accidents with a combined death toll of 6,412. Deaths from military aviation were not included in the study. Occurring most frequently, the statisticians report, are conflagrations, burns, and explosions, with motor vehicle accidents ranking second.

Report of Research Fund.—The Jane Coffin Childs Memorial Fund for Medical Research announces that in a total of $254,587 for support of cancer research projects and fellowships, grants of $10,000 and over were made as follows: Dr. Harry S. N. Greene, Yale University, New Haven, Conn., $76,392 for three years for the biological study of cancer; Edward L. Tatum, Ph.D., Stanford University School of Medicine, San Francisco, $15,000 for three years for studies on biological and enzymatic effects of chemical carcinogens in inducing mutations; Yale University School of Medicine, $10,000 for one year for maintenance of the new animal house; Dr. Leon L. Miller, University of Rochester School of Medicine and Dentistry, $45,000 for three years for studies of protein synthesis as related to neoplastic growth; Dr. Heinz Herrmann, University of Colorado School of Medicine, Denver, $24,500 for three years for studies on the incorporation of radioactive tracer substances into fractions of developing muscle tissue, and Charles W. Hooker, Ph.D., University of North Carolina School of Medicine, Chapel Hill, $12,000 for three years for studies on testicular tumors in mice and the problem of the nature of the tumor cell. Grants of $5,000 to $10,000 include Dr. Alexander Haddow and his associates, Chester Beatty Research Institute of the Royal Cancer Hospital, London, England, $5,000 for a year for investigations on the chemistry, virology, and chemotherapy of cancer; William U. Gardner, Ph.D., and John J. Trentin, Ph.D., Yale University School of Medicine, $5,500 for one year for studies on the endocrine physiology of the growth and function of the mammary gland, lactation, and experimental tumorigenesis; Dr. Henry D. Hoberman, Yale University School of Medicine, $9,900 for one year for investigations on the rates of formation of nuclear and cytoplasmic proteins; Dr. Henry S. Kaplan, Stanford University School of Medicine, San Francisco, $7,150 for one year for studies on the factors controlling growth and metastasis of transplanted tumors, and Dr. Martin Lubin, Massachusetts Institute of Technology, Cambridge, under the guidance of Francis O. Schmitt, Ph.D., $5,500 for one year.

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Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States in the weeks ended as indicated:

Area	Aug. 18, 1951	Aug. 11, 1951	Aug. 19, 1950
New England States			
Maine	6	5	3
New Hampshire	1	5	..
Vermont	6	1	2
Massachusetts	29	26	17
Rhode Island	1	..	2
Connecticut	16	25	12
Middle Atlantic States			
New York	103	105	191
New Jersey	22	10	42
Pennsylvania	49	25	69
East North Central States			
Ohio	95	73	83
Indiana	29	16	29
Illinois	151	129	104
Michigan	117	115	83
Wisconsin	84	57	21
West North Central States			
Minnesota	39	19	22
Iowa	57	33	46
Missouri	50	26	32
North Dakota	6	2	5
South Dakota	7	3	11
Nebraska	21	25	20
Kansas	62	30	18
South Atlantic States			
Delaware	..	..	3
Maryland	4	7	27
District of Columbia	1	3	10
Virginia	14	18	68
West Virginia	8	12	17
North Carolina	23	16	59
South Carolina	17	7	21
Georgia	42	38	18
Florida	15	20	19
East South Central States			
Kentucky	22	17	42
Tennessee	43	51	36
Alabama	54	71	27
Mississippi	40	28	15
West South Central States			
Arkansas	34	18	17
Louisiana	51	36	17
Oklahoma	48	49	23
Texas	95	97	113
Mountain States			
Montana	6	1	1
Idaho	5	5	2
Wyoming	4	3	4
Colorado	82	112	13
New Mexico	4	3	2
Arizona	19	20	1
Utah	50	34	4
Nevada	3	2	..
Pacific States			
Washington	16	19	25
Oregon	6	16	29
California	108	89	63
Territories and Possessions			
Alaska	..	1	..
Hawaii	..	3	..
United States	1,765	1,526	1,485

FOREIGN

European Congress of Rheumatology.—This congress, organized by the Sociedad Espanola de Reumatismo, will be held in Barcelona, Spain, Sept. 24-27 under the sponsorship of the Ministro de la Gobernacion. Dr. Philip S. Hench of the Mayo Clinic, Rochester, Minn., has been officially invited by the Spanish Government as guest of honor.

The Conferences of Bichat.—The discussions of Bichat, "Les Entretiens de Bichat 1951," which have been held during the last four years, will be held Oct. 8-13 at the Faculty of Medicine of Paris. Physicians, surgeons, and specialists will discuss clinical and therapeutic improvements. The first and last days will be reserved, as is customary, for surgeons and specialists, while the other four days will be devoted to physicians and practitioners. The latter will also be able to attend those lectures on surgery and the specialities which are of interest in general practice. Medical motion pictures will be shown during the intermissions for meals and in the evening. The lectures on medicine will be under the direction of professors Guy-Laroche and Justin-Besançon, and those on surgery and specialities under the direction of the surgeons and specialists of the Hôpital Bichat. Registration for the Entretiens de Bichat 1951 may be made at Entretiens de Bichat, L'Expansion Scientifique Francaise, 23, rue du Cherche-Midi, Paris 6e, France.

CORRECTION

Prolapse of the Urethra in Young Girls.—In the article on prolapse of the urethra by Drs. J. Denny Moffett and Rafe Banks Jr. in THE JOURNAL, Aug. 4, 1951 (page 1288), the address of the senior author was omitted. Dr. Moffett's address is 111 Broadway, Daytona Beach, Fla.

MEETINGS

AMBULATORY FRACTURE ASSOCIATION, Arrowhead Springs Hotel, San Bernardino, Calif., Oct. 8-11. Dr. H. W. Wellmerling, 626 Griesheim Bldg., Bloomington, Ill., Secretary.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, Chicago, Oct. 14-18. Dr. W. L. Benedict, 100 First Avenue Bldg., Rochester, Minn., Executive Secretary.

AMERICAN ACADEMY OF PEDIATRICS, Toronto, Canada, Oct. 20-25. Dr. E. H. Christopherson, 636 Church St., Evanston, Ill., Executive Secretary.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA, The Seigniory, Montebello, Quebec, Canada, Oct. 23-25. Dr. Charles G. Johnston, 1512 St. Antoine St., Detroit 26, Secretary.

AMERICAN ASSOCIATION OF BLOOD BANKS, Hotel Nicollet, Minneapolis, Oct. 22-24. Miss Marjorie Saunders, 3301 Junius St., Dallas 1, Texas, Secretary.

AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS AND ABDOMINAL SURGEONS, The Homestead, Hot Springs, Va., Sept. 6-8. Dr. William F. Mengert, 2211 Oak Lawn Ave., Dallas, Texas, Secretary.

AMERICAN CANCER SOCIETY, New York, Oct. 25. Dr. Charles S. Cameron, 47 Beaver St., New York, Medical Director.

AMERICAN CONGRESS OF PHYSICAL MEDICINE, Shirley-Savoy Hotel, Denver, Sept. 4-8. Dr. Walter J. Zeiter, 2020 E. 93d St., Cleveland 6, Executive Director.

AMERICAN HOSPITAL ASSOCIATION, St. Louis, Sept. 17-20. Mr. George Bugbee, 18 E. Division St., Chicago 10, Executive Director.

AMERICAN MEDICAL WRITERS' ASSOCIATION, Pere Marquette Hotel, Peoria, Ill., Sept. 19. Dr. Harold Swanberg, 209 W.C.U. Bldg., Quincy, Ill., Secretary.

AMERICAN ROENTGEN RAY SOCIETY, Washington, D. C., Sept. 25-28. Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Secretary.

AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS, Chicago, Oct. 15-20. Dr. Clyde G. Culbertson, 1040 W. Michigan St., Indianapolis 7, Secretary.

AMERICAN SOCIETY OF MAXILLOFACIAL SURGEONS, Drake Hotel, Chicago, Sept. 23-26. Dr. Casper M. Epsteen, 25 E. Washington St., Chicago 2, Secretary.

ASSOCIATION OF LIFE INSURANCE MEDICAL DIRECTORS OF AMERICA, New York, Oct. 11-12. Dr. Henry B. Kirkland, P. O. Box 594, Newark 1, N. J., Secretary.

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES, Palmer House, Chicago, Oct. 8-10. Colonel James M. Phalen, Armed Forces Institute of Pathology, Washington 25, D. C., Secretary.

CENTRAL NEUROPSYCHIATRIC ASSOCIATION, Hotel Nicollet, Minneapolis, Oct. 19-20. Dr. Lee M. Eaton, 102 Second Ave. S.W., Rochester, Minn., Secretary.

COLLEGE OF AMERICAN PATHOLOGISTS, Chicago, Oct. 15-16. Dr. Tracy B. Mallory, Massachusetts General Hospital, Boston, Secretary.

COLORADO STATE MEDICAL SOCIETY, Denver, Sept. 18-21. Mr. Harvey T. Sethman, 1612 Tremont Place, Denver 2, Executive Secretary.

DELAWARE, MEDICAL SOCIETY OF, Wilmington, Oct. 8-10. Dr. Andrew H. Gehret, 1007 Park Place, Wilmington, Secretary.

DISTRICT OF COLUMBIA, MEDICAL SOCIETY OF THE, Hotel Statler, Washington, Oct. 1-3. Mr. Theodore Wiprud, 1718 M St. N.W., Washington, Secretary.

GULF COAST CLINICAL SOCIETY, Edgewater Gulf Hotel, Edgewater Park, Miss., Oct. 18-19. Dr. C. D. Taylor, 113 Davis Ave., Pass Christian, Miss., Secretary.

INTERSTATE POST GRADUATE MEDICAL ASSOCIATION OF NORTH AMERICA, St. Louis, Oct. 22-26. Dr. Tom B. Throckmorton, Equitable Bldg., Des Moines, Iowa, Secretary.

KANSAS CITY SOUTHWEST CLINICAL SOCIETY, Municipal Auditorium, Kansas City, Mo., Oct. 1-4. Dr. Maxwell G. Berry, 630 Shukert Bldg., Kansas City, Mo., Director of Clinics.

KENTUCKY STATE MEDICAL ASSOCIATION, Columbian Auditorium, Louisville, Oct. 2-5. Dr. Bruce Underwood, 620 S. Third St., Louisville 2, Secretary.

MICHIGAN STATE MEDICAL SOCIETY, Grand Rapids, Sept. 26-28. Dr. L. Fernald Foster, 606 Townsend St., Lansing 15, Secretary.

MIDWEST REGIONAL MEETING AMERICAN COLLEGE OF PHYSICIANS, Columbus, Ohio, Oct. 13. Dr. B. K. Wiseman, Kinsman Hall, Ohio State University, Columbus 10, Ohio, Chairman.

MISSISSIPPI VALLEY MEDICAL SOCIETY, Peoria, Ill., Sept. 19-21. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

MONTANA MEDICAL ASSOCIATION, Great Falls, Sept. 13-16. Mr. L. R. Hegland, 104 N. Broadway, Billings, Executive Secretary.

NASHVILLE POSTGRADUATE MEDICAL ASSEMBLY, Maxwell House, Nashville, Tenn., Oct. 3-5. Dr. W. G. Kennon Jr., 647 Doctors Bldg., Nashville 3, Secretary.

NEUROSURGICAL SOCIETY OF AMERICA, Sun Valley, Idaho, Sept. 12-14. Dr. C. D. Hawkes, 22 N. Manassas St., Memphis 5, Tenn., Secretary.

NEVADA STATE MEDICAL ASSOCIATION, Riverside Hotel, Reno, Sept. 13-15. Dr. Wesley W. Hall, 307 W. Sixth St., Reno, Secretary.

NEW HAMPSHIRE MEDICAL SOCIETY, Equinox House, Manchester, Vermont, Sept. 30-Oct. 2. Dr. Deering G. Smith, 44 Chester St., Nashua, Secretary.

NORTHEASTERN SECTION, SOUTHEASTERN SURGICAL CONGRESS, Lord Baltimore Hotel, Baltimore, Sept. 13-15. Dr. W. Raymond McKenzie, Medical Arts Bldg., Baltimore 1, Secretary.

NORTH TEXAS-SOUTHERN OKLAHOMA FALL CLINICAL CONFERENCE, Wichita Falls, Texas, Sept. 19. Dr. W. L. Powers, 517 Hamilton Bldg., Wichita Falls, Chairman.

OREGON STATE MEDICAL SOCIETY, Masonic Temple, Portland, Oct. 10-13. Dr. Robert F. Miller, 833 S.W. Eleventh Ave., Portland 5, Secretary.

PENNSYLVANIA, MEDICAL SOCIETY OF THE STATE OF, Pittsburgh, Sept. 16-20. Dr. Walter F. Donaldson, 500 Penn Ave., Pittsburgh 22, Secretary.

SOUTHWESTERN MEDICAL ASSOCIATION, El Paso, Texas, Oct. 18-20. Dr. W. W. Schuessler, 1415 First National Bank Bldg., El Paso, Texas, Secretary.

SOUTHWESTERN SURGICAL CONGRESS, Hotel Jefferson, St. Louis, Sept. 24-26. Dr. C. R. Rountree, 1227 Classen St., Oklahoma City 3, Secretary.

TEXAS ACADEMY OF GENERAL PRACTICE, Shamrock Hotel, Houston, Texas, Sept. 10-11. Dr. B. H. Bayer, 104 E. 20th St., Houston 8, Secretary.

U. S. CHAPTER, International College of Surgeons, Palmer House, Chicago, Sept. 10-14. Dr. Arnold S. Jackson, 1516 Lake Shore Drive, Chicago, Executive Secretary.

UTAH STATE MEDICAL ASSOCIATION, Salt Lake City, Sept. 13-15. Dr. T. C. Weggeland, 42 S. Fifth East St., Salt Lake City, Secretary.

VERMONT STATE MEDICAL SOCIETY. Equinox House, Manchester, Sept. 30-Oct. 2. Dr. James P. Hammond, 542 Main St., Bennington, Secretary.

VIRGINIA, MEDICAL SOCIETY OF, Virginia Beach, Oct. 7-10. Mr. Richard H. Nash, 1105 W. Franklin St., Richmond, Executive Secretary.

WASHINGTON STATE MEDICAL ASSOCIATION, Olympic Hotel, Seattle, Sept. 9-12. Dr. James W. Haviland, 338 White-Henry-Stuart Bldg., Seattle, Secretary.

WESTERN SOCIETY OF ELECTRO-ENCEPHALOGRAPHY, Olympic Hotel, Seattle, Sept. 7-8. Dr. Nicholas A. Bercel, 450 N. Bedford Drive, Beverly Hills, Calif., Secretary.

WISCONSIN, STATE MEDICAL SOCIETY OF, Hotel Schroeder and Milwaukee Auditorium, Milwaukee, Oct. 1-3. Mr. Charles H. Crownhart, 704 E. Gorham St., Madison 3, Secretary.

WYOMING STATE MEDICAL SOCIETY, Rock Springs, Sept. 27-29. Dr. Glenn W. Koford, 2020 Carey Ave., Cheyenne, Secretary.

INTERNATIONAL

EUROPEAN CONGRESS ON RHEUMATISM, Barcelona, Spain, Sept. 24-27. Dr. Gunnar Edström, Lund, Sweden, Secretary.

GENERAL PRACTITIONERS STUDY CLUB INTERNATIONAL, Rome, Italy, Sept. 12-15. Dr. John O'Connell, 10300 Lackland Road, St. Louis 14, Mo., U. S. A., President.

INTER-AMERICAN CONGRESS OF SURGERY, Buenos Aires, Argentina, Oct. 1-6.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, London, England, Sept. 3-7. Mr. R. W. Cope, University College Hospital, London W.C.1, England.

INTERNATIONAL ASSOCIATION OF ALLERGISTS, Zurich, Switzerland, Sept. 23-29. Prof. A. S. Grumbach, Hygiene Institut der Universitaet Zurich, Gloriastr. 32, Zurich, Switzerland.

INTERNATIONAL CONGRESS OF ANESTHESIOLOGY, Nursing School of the Salpiettre, 47 Boul de l'Hospital, Paris, France, Sept. 20-22. 12 rue de Seine, Paris 6e, France, Secretariat.

INTERNATIONAL CONGRESS ON INDUSTRIAL MEDICINE, Instituto Superior Técnico, Lisbon, Portugal, Sept. 9-15. Dr. Luis Guerreiro, Instituto Nacional do Trabalho e Previdência, Praça do Comercio, Lisbon, Secretary General.

INTERNATIONAL CONGRESS ON MENTAL HEALTH, Mexico City, Mexico, Dec. 11-19. Mrs. Grace E. O'Neill, Division of World Affairs, National Association on Mental Health, 1790 Broadway, New York 19, N. Y.

INTERNATIONAL GERONTOLOGICAL CONGRESS, Hotel Jefferson, St. Louis, Mo., U. S. A., Sept. 9-14. Dr. John E. Kirk, 5600 Arsenal Street, St. Louis 9, Mo., Chairman, Program Committee.

INTERNATIONAL POLIOMYELITIS CONGRESS, Copenhagen, Denmark, Sept. 3-7. Prof. Dr. Niels Bohr, Statens Seruminstitut, 80 Amager Blvd., Copenhagen S., Denmark, President.

INTERNATIONAL SOCIETY OF SURGERY, Paris, France, Sept. 24-29. Dr. L. Dejardin, 141, rue Belliard, Brussels, Belgium, Secretary General.

INTERNATIONAL SOCIETY FOR THE WELFARE OF CRIPPLES, Fifth World Congress, Stockholm, Sweden, Sept. 9-14. Mr. Donald V. Wilson, 54 E. 64th St., New York 21, N. Y., U. S. A., Executive Director.

PAN AMERICAN CONGRESS OF PEDIATRICS, Montevideo, Uruguay, Dec. 5-8. Dr. Maria Luisa Saldien de Rodriguez, Avenida 18 de Julio, 1246, Montevideo, Uruguay, General Secretary.

PAN PACIFIC SURGICAL ASSOCIATION CONGRESS, Honolulu, Hawaii, Nov. 7-19. Dr. Forrest J. Pinkerton, Suite 7, Young Bldg., Honolulu, Hawaii, President.

WORLD CONFEDERATION FOR PHYSICIAL THERAPY, Copenhagen, Denmark, Sept. 7-8.

WORLD MEDICAL ASSOCIATION, Stockholm, Sweden, Sept. 15-21. Dr. Louis H. Bauer, 2 E. 103d St., New York 29, N. Y., U. S. A., Secretary General.

EXAMINATIONS AND LICENSURE

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 24-26, 1952. Sec., Dr. D. G. Gill, 537 Dexter Ave., Montgomery 4.

ARKANSAS:* *Regular.* Little Rock, Nov. 8-9. Sec., Dr. Joe Verser, Harrisburg.

COLORADO:* *Reciprocity.* Denver, Oct. 9. Final date for filing application is Sept. 24. Ex. Sec., Mrs. Beulah H. Hudgens, 831 Republic Bldg., Denver 2.

GEORGIA: Atlanta, June. August, Oct. 9-11. Sec., Mr. R. C. Coleman, 111 State Capitol, Atlanta.

GUAM: The Commission on Licensure will meet whenever a candidate appears or submits his credentials. Ex. Sec., Dr. John Y. Battenfield, Agana.

ILLINOIS: Chicago, Oct. 9-11. Superintendent of Registration, Mr. Charles F. Kervin, Capitol Building, Springfield.

INDIANA: Indianapolis, June 1952. Sec., Dr. Paul R. Tindall, 1138 K of P Bldg., Indianapolis 4.

KANSAS: Topeka, Dec. 12-13. Sec., Dr. O. W. Davidson, 772 New Brotherhood Bldg., Kansas City.

KENTUCKY: *Examination.* Louisville, Dec. 11-13. Sec., Dr. Bruce Underwood, 620 S. 3rd St., Louisville.

MARYLAND: *Examination.* Baltimore, Dec. 11-14. Sec., Dr. Lewis P. Gundry, 1215 Cathedral St., Baltimore.

MICHIGAN:* *Examination.* Lansing, Oct. 10-12. Sec., Dr. J. Earl McIntyre, 202-4 Hollister Bldg., Lansing.

MINNESOTA:* Minneapolis, Oct. 16-18. Sec., Dr. Julian F. DuBois, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: *Reciprocity.* Jackson, December. Asst. Sec., Dr. R. N. Whitfield, Old Capitol Bldg., Jackson.

NEW HAMPSHIRE: Concord, Sept. 12-13. Sec., Dr. John Samuel Wheeler, Room 107 State House, Concord.

NEW JERSEY: *Examination.* Trenton, Oct. 16-19. Sec., Dr. E. S. Hallinger, 28 W. State St., Trenton.

NEW MEXICO:* Santa Fe, Oct. 8-9. Sec., Dr. Charles J. McGoey, Coronado Bldg., Santa Fe.

NEW YORK: *Examination.* Albany, Buffalo, New York and Syracuse, Oct. 31-Nov. 3. Sec., Dr. Jacob L. Lochner, Jr., 23 S. Pearl St., Albany.

NORTH CAROLINA: Asheville, Oct. 7-8. Sec., Dr. Joseph J. Combs, Professional Bldg., Raleigh.

OHIO: *Examination.* Columbus, December. *Reciprocity.* Columbus, Oct. 2. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus 15.

OREGON:* *Reciprocity.* Portland, Oct. 12-13. *Examination.* Portland, Jan. 1952. Ex. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

PUERTO RICO: *Examination.* Santurce, Sept. 4-7. Sec., Mr. Luis Cueto Coll, Box 3717, Santurce.

SOUTH CAROLINA: *Reciprocity.* Columbia, Sept. 10 and Oct. 1. Sec., Dr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination.* Sioux Falls, Jan. 15-16. Ex. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

VIRGIN ISLANDS: Charlotte Amalie, Nov. 7-8. Sec., Dr. Earle M. Rice, St. Thomas.

WYOMING: *Examination.* Cheyenne, Oct. 1. Sec., Dr. Franklin D. Yoder, State Capitol, Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARIZONA: *Examination.* Tucson, Sept. 18. Sec., Mr. Francis A. Roy, 423 Liberal Arts Bldg., University of Arizona, Tucson.

CONNECTICUT: *Examination.* New Haven, Oct. 13. Exec. Asst., Miss Mary G. Reynolds, State Board of Healing Arts, 110 Whitney Avenue, New Haven 10.

DISTRICT OF COLUMBIA: *Examination.* Washington, Oct. 22-23. Sec., Dr. Daniel L. Seckinger, 4130 E. Municipal Bldg., Washington.

FLORIDA: Gainesville, Nov. 10. Sec., Mr. M. W. Emmel, Box 340, University of Florida, Gainesville.

MICHIGAN: Detroit and Ann Arbor, Oct. 12-13. *Examination.* Sec., Miss Eloise LeBeau, 501 W. Michigan Ave., Lansing 15.

MINNESOTA: *Examination.* Minneapolis, Oct. 2-3. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis.

NEBRASKA: *Examination.* Omaha, Oct. 2-3. Director, Bureau of Examining Boards, Mr. Oscar F. Humble, Room 1009, State Capitol Bldg., Lincoln 9.

OKLAHOMA: Oklahoma City, Sept. 14. Sec., Dr. Frank C. Gallaher, 813 Braniff Bldg., Oklahoma City 4.

OREGON: *Examination.* Portland, Sept. 8 and Dec. 1. Sec., Dr. Charles D. Byrne, State Board of Higher Education, University of Oregon, Eugene.

SOUTH DAKOTA: *Examination.* Vermillion, Dec. 7-8. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

TEXAS: *Examination.* Austin, October. Chief Clerk, Mr. B. H. Kirk, 306 Nalle Bldg., Austin.

WISCONSIN: *Examination.* Madison, Sept. 22. Sec., Mr. W. H. Barber, Ripon College, Ripon.

* Basic Science Certificate required.

DEATHS

Paullin, James Edgar ⊕ President of the American Medical Association, 1943-1944, died at his home in Atlanta, Aug. 13, aged 69, of a heart attack. Dr. Paullin was born in Fort Gaines, Ga., Nov. 3, 1881. After graduation from Mercer University with the degree of bachelor of arts in 1900, he continued as a graduate student throughout 1901 and then entered Johns Hopkins University School of Medicine, from which he received the degree of doctor of medicine in 1905. He also held LL.D. degrees from Mercer and Emory universities. He turned briefly to pathology, acting as resident pathologist of the Rhode Island Hospital in Providence from 1905 to 1906, as resident in the Piedmont Hospital in 1906-1907, as pathologist to the Georgia State Board of Health from 1907 to 1911, and at the same time as associate professor of pathology of the Atlanta College of Physicians and Surgeons. In 1909 he first turned his attention to internal medicine, acting as associate visiting physician to Grady Hospital from 1909 to 1913, and as adjunct professor of medicine at Atlanta Medical College from 1913 to 1915. With the outbreak of World War I Dr. Paullin became a major in the Medical Corps of the United States Army and served as chief of the medical service in Camp Shelby, Miss. He was a specialist certified by the American Board of Internal Medicine. In the field of medical organizations he had come through the ranks of organized medicine, having been president of his county medical society in 1913 and of the Medical Association of Georgia, Chairman of the Section on Practice of Medicine of the American Medical Association in 1928, a member of the Council on Scientific Assembly from 1933 to 1942, serving as its chairman since 1937, and finally President of the American Medical Association in 1943. In the House of Delegates, where he had represented the Section on Practice of Medicine, he had been a member of many important reference committees as well as a member of the Committee on Medical Preparedness. He was a fellow of the American College of Physicians, of which he had been president, and had served as master and at various times as regent and chairman of various committees. Active in other scientific organizations, he served as president of the American Clinical and Climatological Society in 1937 and of the Interstate Postgraduate Medical Association 1946-1947, and as chairman of the Medical Section of the Southern Medical Association. He was a member of the Association of American Physicians, since 1944 a corresponding member of the Society of Internal Medicine, Buenos Aires, and a member of the medical board of the National Foundation for Infantile Paralysis. His eminence had been recognized by his election to Alpha Omega Alpha, and he had been guest professor of medicine at Peter Bent Brigham Hospital and at the Pratt Diagnostic Clinic of Tufts College Medical School in Boston. With the beginning of preparations for World War II he was called early to the work of the Division of Medical Sciences of the National Research Council and gave largely of his time to the classification of specialists in the field of internal medicine. In 1947 the President of the United States awarded him the Medal for Merit. The citation specified exceptionally meritorious conduct in the performance of outstanding services to the United States since 1943 and explained that Dr. Paullin served as honorary consultant to the Bureau of Medicine and Surgery of the Navy Department while also serving as a member of the directing board of the Procurement and Assignment Service of the War Manpower Commission. Early in 1942 he had gone to Cuba to aid in the organization of the Finlay Institute of the Americas for securing interchange of medical science with the Latin American countries. He was decorated by President Batista with the Order of Carlos Finlay. In 1944 the Atlanta Chamber of Commerce awarded its annual Certificate of Distinguished Achievement to Dr. Paullin. In 1947 he was appointed a member of the Federal Hospital Council of the U. S. Public Health Service. His scientific contributions included many papers published in leading periodicals. At the time of his death Dr. Paullin was a consultant for the Council on National Emergency Medical Service, American Medical Association; professor of clinical medicine at Emory University School of Medicine, visiting physician at Grady Hospital, and consulting physician at Piedmont Hospital.

JAMES EDGAR PAULLIN
1881-1951

⊕ Indicates Fellow of the American Medical Association.

Lewis, Frederic Thomas, Boston; born in Cambridge, Mass., March 18, 1875; Harvard Medical School, Boston, 1901; from 1901 to 1902 Austin fellow in histology and embryology at his alma mater, where he continued as instructor from 1902 to 1906, assistant professor from 1906 to 1915, associate professor of embryology from 1915 to 1931, and James Stillman professor of comparative anatomy from 1931 to 1941, when he became James Stillman professor of comparative anatomy emeritus; member and past president and vice president of the American Association of Anatomists; at one time vice president of the Boston Society of Natural History; fellow of the American Academy of Arts and Sciences and the American Association for the Advancement of Science; co-author of "Text-Book of Histology"; died June 2, aged 76, of coronary thrombosis.

Arkin, Harry Samuel ⊕ Chicago; born April 22, 1893; Rush Medical College, Chicago, 1917; assistant professor of medicine at Northwestern University Medical School; specialist certified by the American Board of Internal Medicine; member of the American College of Chest Physicians and the American Trudeau Society; served on the staffs of the Veterans Administration Hospital in Hines, Winfield (Ill.) Tuberculosis Sanitarium, Cook County Hospital, Columbus Memorial Hospital, and Michael Reese Hospital, where he died July 8, aged 58, of coronary thrombosis.

Arvin, Hugh Torrance, Los Angeles; Bellevue Hospital Medical College, New York, 1892; at one time practiced in Greenville, Texas, where he was city physician, and served on the public school board; affiliated with California Hospital, Los Angeles General Hospital, and Angelus Hospital; died June 16, aged 81, of cerebral vascular accident.

Bennett, Edward Calvin, Ukiah, Calif.; College of Physicians and Surgeons, Baltimore, 1912; member of the American Medical Association; past president of the Mendocino County Medical Association; received a presidential citation for his service as a member of the Selective Service during World War II; for the past six years did psychiatric work for the superior courts of Sonoma and Mendocino counties; died in Ukiah General Hospital, June 12, aged 62, of peptic ulcer and peritonitis.

Block, Jacob M. ⊕ Ridgewood, N. Y.; Long Island College Hospital, Brooklyn, 1921; served on the staffs of the Wyckoff Heights and Bethany Deaconess hospitals in Brooklyn; past president of the Long Island College Alumni; died June 2, aged 51, of coronary insufficiency.

Bookstaver, Barnet Seymour, Teaneck, N. J.; University and Bellevue Hospital Medical College, New York, 1908; member of the American Medical Association; served as director of health, medical director of schools, health officer, and police and fire surgeon; affiliated with Lebanon Hospital in New York and Holy Name Hospital; died June 26, aged 64, of coronary occlusion.

Brandt, Herman D., St. Louis; Washington University School of Medicine, St. Louis, 1891; died June 16, aged 82, of cerebral hemorrhage.

Bromley, Anthony Wayne, Louisa, Ky.; Eclectic Medical Institute, Cincinnati, 1898; member of the American Medical Association; vice president of the First National Bank of Louisa; died June 17, aged 81.

Burkel, Arthur Jacob ⊕ Buffalo; University of Buffalo School of Medicine, 1915; member of the Selective Service boards in his area during World Wars I and II; on the staff of Millard Fillmore Hospital; died in Peter Bent Brigham Hospital, Boston, June 15, aged 59, of acute myocardial infarction.

Burns, James Edwin, Huntington Park, Calif.; University of California Medical School, San Francisco, 1933; member of the American Medical Association; affiliated with Mission Hospital and with St. Francis Hospital in Lynwood; died June 19, aged 46, of spontaneous subarachnoid hemorrhage.

Campbell, Arthur Lindly ⊕ Hatboro, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1927; served on the school board; died June 4, aged 51, of coronary disease.

Cerswell, Benjamin Samuel, Yakima, Wash.; University of Toronto Faculty of Medicine, Toronto, Canada, 1907; member of the American Medical Association; died June 23, aged 77, of coronary insufficiency, carcinoma of the prostate, and diabetes mellitus.

Clohessy, Timothy Theodore ⊕ Phoenix, Ariz.; University of Buffalo School of Medicine, 1894; died June 20, aged 78, of bronchogenic carcinoma.

Curtin, John Francis, North Abington, Mass.; Baltimore Medical College, 1906; member of the American Medical Association; served as medical examiner of the second Plymouth district; died June 4.

DaHinden, Frank, Canton, Ohio; University of Wooster Medical Department, Cleveland, 1898; formerly health commissioner of Canton; died in State Hospital, Massillon, June 13, aged 76, of acute coronary insufficiency.

Davis, John Allen, Roanoke, Va.; University of Maryland School of Medicine, Baltimore, 1889; died June 19, aged 84, of kidney tumor.

Davison, Glenn Huston ⊕ Pittsburgh; University of Pittsburgh School of Medicine, 1919; associate professor of urology at his alma mater; specialist certified by the American Board of Urology; member of the American Urological Association; fellow of the American College of Surgeons; affiliated with St. Francis Hospital, where he died June 3, aged 60, of leukemia.

Dingman, Cecil Walker ⊕ Major, U. S. Army, retired, San Francisco; University of Nebraska College of Medicine, Omaha, 1925; entered the medical corps of the regular army as a first lieutenant in July 1926; became a major in 1937; retired on April 30, 1942, for disability in line of duty; medical examiner for the United Air Lines; killed in an airplane crash June 29, aged 51.

Donahoe, John Patrick ⊕ Scranton, Pa.; Jefferson Medical College of Philadelphia, 1904; also a graduate in pharmacy; served during World War I; consultant at West Side Hospital; affiliated with Mercy, St. Mary's, and Scranton State hospitals; died June 4, aged 75, of carcinoma of the colon.

Edgerton, Andrew Clifford, Clio, Mich.; Detroit College of Medicine and Surgery, 1919; served on the staffs of Hurley Hospital and St. Joseph Hospital in Flint; died in Alabaster June 24, aged 60, of coronary thrombosis.

English, Glenn Greer ⊕ Captain, U. S. Navy, retired, North Hollywood, Calif.; Indiana University School of Medicine, Indianapolis, 1922; served during World War II; retired May 1, 1949; died in San Fernando June 9, aged 53, of tuberculosis.

Enselberg, Herman L. ⊕ Long Island City, N. Y.; University and Bellevue Hospital Medical College, New York, 1919; assistant clinical professor of obstetrics and gynecology at New York Medical College, Flower and Fifth Avenue Hospitals, New York; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; affiliated with Queens General Hospital in Jamaica; died June 15, aged 54.

Farver, Moses A. ⊕ Middlebury, Ind.; Baltimore Medical College, 1893; Associate Fellow of the American Medical Association; on the staff of the Elkhart (Ind.) General Hospital; died June 29, aged 84, of mitral stenosis.

Fredrickson, Frederick Olaf ⊕ Chicago; Rush Medical College, Chicago, 1908; assistant professor of medicine, emeritus, at the University of Illinois College of Physicians and Surgeons; fellow of the American College of Physicians; specialist certified by the American Board of Internal Medicine; past president of the Illinois State Medical Society; served during World War I; formerly on the staff of Ravenswood Hospital; died July 6, aged 76.

Gaffney, Emory Clizbe ⊕ Lincoln, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1905; member of the American Association of Railway Surgeons and the Association of Military Surgeons of the United States; for many years on the elementary grade school board of education, serving as its president; served during World War I; past president of the Logan County Medical Society; affiliated with Evangelical Deaconess Hospital, where he died June 1, aged 66, of nephritis.

Gerard, Gabriel R., Chickasha, Okla.; University Medical College of Kansas City, Mo., 1899; died in Madonna Hospital, Denison, Texas, May 8, aged 80.

Gray, James Anthony, Watson, Mo.; Central Medical College of St. Joseph, 1903; served for two terms in the state house of representatives; died in Jefferson City June 6, aged 68, of coronary thrombosis.

Harris, Emanuel, Somerset, Mass.; Long Island College Hospital, Brooklyn, 1894; formerly city physician in Fall River; died in Truesdale Hospital, Fall River, July 5, aged 79, of cardiorenal disease.

Heck, Ruth Elizabeth Vories, Rochester, Minn.; University of Minnesota Medical School, Minneapolis, 1926; certified by the National Board of Medical Examiners; entered the Mayo Foundation as a fellow in pediatrics in October, 1926, and left the Mayo Foundation in April, 1928; died June 18, aged 57, of cardiac failure.

Hedger, Caroline, Clinton, Conn.; Northwestern University Woman's Medical School, Chicago, 1899; Rush Medical College, Chicago, 1904; for many years medical consultant for the Elizabeth McCormick Memorial Fund in Chicago; died July 10, aged 83, of Parkinson's disease and arteriosclerosis.

Heksh, Bela Hajos, New York; Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest, Hungary, 1913; member of the American Medical Association, American Psychoanalytic Association, and the American Psychiatric Association; served as a captain in the Austro-Hungarian Army during World War I; died June 11, aged 61.

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Higgins, Herbert Albert, Ardmore, Okla.; Dallas Medical College, 1904; member of the American Medical Association; affiliated with Ardmore Sanitarium and Hospital and Hardy Sanitarium; died June 4, aged 77, of coronary occlusion.

Hines, Julius Charles ✠ Brooklyn; Meharry Medical College, Nashville, Tenn., 1933; affiliated with Unity Hospital, where he died June 1, aged 45, of coronary thrombosis.

Hopkins, Granville A., Glenwood Springs, Colo.; Denver and Gross College of Medicine, 1907; served as county coroner and was registrar of the bureau of vital statistics for the state and was city health officer; died June 2, aged 61, of carcinoma.

Hyman, David Elihu ✠ New York; Columbia University College of Physicians and Surgeons, New York, 1907; formerly on the staff of Mount Sinai Hospital; died June 20, aged 70, of coronary thrombosis.

Igo-Flitcroft, Louise M., Sacramento, Calif.; University of Southern California School of Medicine, Los Angeles, 1906; member of the American Medical Association; died June 9, aged 84, of hypertensive cardiovascular disease and arteriosclerosis.

Jones, Gerald Woodrow, Orlando, Fla.; Emory University School of Medicine, Atlanta, 1943; member of the American Medical Association; formerly secretary of the Orange County Medical Society; served during World War II; on the staff of Orange Memorial Hospital; died June 5, aged 32, of carcinoma of the testicle with metastases.

Jurney, Peter Claywell, Turnersburg, N. C.; Medical College of Virginia, Richmond, 1901; died June 6, aged 76, of heart disease.

Key, Elmore Benjamin, Meridian, Miss.; University of Nashville (Tenn.) Medical Department, 1901; member of the American Medical Association; medical examiner for the aeronautics administration for many years; at one time medical superintendent of the Matty Hersee Hospital; died in Riley's Hospital June 9, aged 73, of arteriosclerosis.

Leach, Sydney, Tuscaloosa, Ala.; University of Virginia Department of Medicine, Charlottesville, 1896; member of the American Medical Association; affiliated with Bryce Hospital; died in Montgomery, in May, aged 76, of pulmonary embolus.

Leavitt, Mary Augusta, Boston; Boston University School of Medicine, 1902; served on the faculty of her alma mater; member of the American Medical Association; died May 2, aged 74.

Lien, Fred Oscar ✠ Merced, Calif.; University of Illinois College of Medicine, Chicago, 1914; served during World War I; on the staffs of Merced General Hospital and Mater Misericordiae Hospital, where he died June 23, aged 64, of carcinoma of the colon.

Lindquist, Gustav Herman, Worcester, Mass.; Middlesex University School of Medicine, Waltham, 1919; on the staff of the Fairlawn Hospital; died in City Hospital June 30, aged 69, of cerebral vascular accident.

Loftis, William Osler ✠ Alexandria, La.; University of Arkansas School of Medicine, Little Rock, 1934; member of the Arkansas Medical Society; served during World War II; affiliated with the Veterans Administration Hospital, where he died May 12, aged 41.

Lupton, Albert Marsee ✠ Philadelphia; Jefferson Medical College of Philadelphia, 1939; specialist certified by the American Board of Internal Medicine; served during World War II; affiliated with Hahnemann Hospital; died June 28, aged 36.

Macdonald, John William ✠ St. Louis; St. Louis University School of Medicine, 1905; an Associate Fellow of the American Medical Association; served during the Spanish-American War and World War I; died in Christiansted, Virgin Islands, June 3, aged 73, of cerebral hemorrhage.

MacNaughton, Luther Donald, Eagle Grove, Iowa; Drake University Medical Department, Des Moines, 1897; member of the American Medical Association; died in Fort Dodge June 11, aged 80, of carcinoma of the prostate.

MacLean, Lester, Chicago; University of Minnesota Medical School, Minneapolis, 1943; member of the American Medical Association; specialist certified by the American Board of Psychiatry and Neurology; assistant professor of psychiatry at the University of Illinois College of Medicine; a founder of the Park Forest school district; served during World War II; accidentally drowned at Farm Island Lake near Aitken, Minn., July 6, aged 33.

Mahoney, Charles Frederick, Winthrop, Mass.; Tufts College Medical School, Boston, 1906; member of the American Medical Association; served on the board of health and as school physician; affiliated with Winthrop Community Hospital; died in Boston June 10, aged 68, of cerebral hemorrhage.

Mann, Ira Thurman ✠ High Point, N. C.; Jefferson Medical College of Philadelphia, 1912; died May 13, aged 62, of coronary thrombosis.

Mantinband, Jacob, New York; Columbia University College of Physicians and Surgeons, New York, 1900; member of the American Medical Association; medical officer for the board of education; affiliated with Gouveneur Hospital, Roosevelt Hospital, and New York Polyclinic Hospital; died June 3, aged 72.

Maples, William Ellis, Athens, Ala.; University of Nashville (Tenn.) Medical Department, 1903; member of the American Medical Association; died in Decatur May 27, aged 76, of coronary occlusion.

Marcou, Louis Benjamin, Berlin, N. H.; University of Vermont College of Medicine, Burlington, 1899; member of the American Medical Association; fellow of the American College of Surgeons; served during World War I; formerly member of the school board; affiliated with St. Louis Hospital, where he died June 14, aged 77, of arteriosclerotic heart disease.

Mars, Jesse Durland, Florida, N. Y.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1904; member of the American Medical Association; health officer and school physician; past president of the Orange County Medical Association; affiliated with the Goshen (N. Y.) Hospital, where he died June 9, aged 70, of coronary thrombosis.

McCracken, Robert X., Belleville, Ill.; St. Louis Medical College, 1890; member of the American Medical Association; formerly county coroner and health commissioner of East St. Louis; died in St. Mary's Hospital, East St. Louis, June 18, aged 87, of cerebral hemorrhage and arteriosclerosis.

McGavern, John Harrison, Honeoye Falls, N. Y.; Syracuse University College of Medicine, 1929; member of the American Medical Association; died in Rochester, N. Y., July 7, aged 48, of myocardial infarction.

McGunagle, Joseph Elmer, Miami, Fla.; Vanderbilt University School of Medicine, Nashville, Tenn., 1912; member of the American Medical Association; died June 5, aged 65, of metastatic carcinoma of the brain.

Merry, Charles Raymond, Washington, D. C.; Meharry Medical College, Nashville, Tenn., 1939; assistant physician on the staff of the Howard University Health Service on a temporary part time basis; died May 28, aged 37, of pulmonary insufficiency.

Mills, Edgar Stuart, Chicago; Rush Medical College, Chicago, 1928; medical director of the Central Standard Life Insurance Company; died June 4, aged 61, of myocardial infarction and coronary sclerosis.

Mitchell, Horace Ervin ✠ Lakewood, Ohio; Jefferson Medical College of Philadelphia, 1912; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, American Laryngological, Rhinological and Otological Society and the American Broncho-Esophagological Association; fellow of the American College of Surgeons; served on the staffs of Fairview Park Hospital in Cleveland and Lakewood Hospital; died June 21, aged 63, of coronary disease.

Montgomery, John W., Birds, Ill.; Hospital College of Medicine, Louisville, Ky., 1897; member of the American Medical Association; died June 22, aged 75, of arteriosclerosis.

Moore, Elisha Merriweather, Prattville, Ala.; University of Alabama School of Medicine, 1911; member of the American Medical Association; served as health officer of Autauga and Chilton counties; died June 21, aged 65.

Morris, Henry Thomas, Greenup, Ky.; Kentucky School of Medicine, Louisville, 1897; member of the American Medical Association; served two terms in the state senate; past president of the Greenup Chamber of Commerce; died May 23, aged 82, of acute cardiac dilatation.

Morris, Julian H., Dallas, Texas.; University of Virginia Department of Medicine, Charlottesville, 1901; member of the American Medical Association; died June 9, aged 70, of heart disease and arteriosclerosis.

Morrison, Hector ✠ Smith Center, Kan.; University of Toronto Faculty of Medicine, Toronto, Canada, 1900; served during World War I; died June 6, aged 81, of coronary thrombosis.

Nelson, Bernard, Chicago; University of the City of New York Medical Department, 1895; died June 15, aged 82, of cerebral hemorrhage and arteriosclerosis.

Nelson, Henry S., ✠ Minneapolis; University of Minnesota College of Medicine and Surgery, Minneapolis, 1893; an Associate Fellow of the American Medical Association; at one time county coroner; died June 8, aged 86, of bronchopneumonia.

Nolan, John William, El Dorado, Ark.; University of Arkansas School of Medicine, Little Rock, 1916; died June 1, aged 70.

Nossen, Herbert Ludwig W. ✠ New York; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1920; member of the Rudolph Virchow Society and the Association for Advancement of Psychotherapy; served with the German Army during World War I; author of "Twelve Against Alcoholism"; died in Beth Israel Hospital June 2, aged 55, of chronic glomerulonephritis.

Nunnery, Ernest Ezra, Everglades, Fla.; University of Nashville (Tenn.) Medical Department, 1907; member of the American Medical Association; served during World War I; lieutenant colonel in the medical reserve corps of the U. S. Army; served in the Veterans Administration in Wichita, Kan., during World War II; physician in charge of Juliet C. Collier Hospital; died in Miami, May 1, aged 66, of coronary occlusion.

Orenstein, Archie ✠ Hilo, Hawaii; University of Pennsylvania School of Medicine, Philadelphia, 1919; served as vice president of the Hawaii Territorial Medical Association; killed in plane crash in Colorado June 29, aged 55.

Ormerod, Henry V., Niles, Ohio; University of Wooster Medical Department, Cleveland, 1898; member of the American Medical Association; affiliated with Trumbull Memorial Hospital, where he died July 3, aged 86, of cerebral vascular disease.

Ossip, Abraham ✠ New York; New York Homeopathic Medical College and Hospital, New York, 1918; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; associate attending radiologist, New York Post Graduate Dispensary; died in Beth Israel Hospital July 3, aged 62, of pulmonary infarction.

Owen, Leartus J. ✠ Colonel, U. S. Army, retired, Charlottesville, Va.; University of Virginia Department of Medicine, Charlottesville, 1900; College of Physicians and Surgeons, Baltimore, 1904; entered the regular army on May 23, 1904; served during World War I; became a colonel in 1930; retired Nov. 30, 1932, for disability in line of duty; fellow of the American College of Surgeons; died in the University of Virginia Hospital June 2, aged 72, of hyperpyrexia.

Padgett, Everett Ervin ✠ Indianapolis; Rush Medical College, Chicago, 1905; assistant professor of surgery at Indiana University School of Medicine; fellow of the American College of Surgeons; past president of the Indiana State Medical Association; at one time president of the city board of health; on the staffs of Indiana University Hospital, St. Vincent's Hospital, General Hospital, and Methodist Hospital, where he died May 24, aged 72, of coronary occlusion.

Palen, Neil Bertram ✠ Walden, N. Y.; Albany (N. Y.) Medical College, 1909; died in St. Luke's Hospital, Newburgh, July 4, aged 68, of chronic coronary insufficiency.

Parsons, Frank Sears, Boston; University of the City of New York Medical Department, New York, 1886; affiliated with Harley Hospital; died in Deaconess Hospital June 4, aged 88, of carcinoma of the prostate.

Partee, William Eugene Jr., Norfolk, Va.; College of Physicians and Surgeons, Boston, 1942; affiliated with Norfolk Community Hospital, died May 13, aged 62.

Peake, William Marion, Long Beach, Calif.; University of Colorado School of Medicine, Denver, 1930; member of the American Medical Association; served during World War II; died in June, aged 45.

Pearson, Walter J., Kansas City, Mo.; University of Kansas School of Medicine, Kansas City, 1907; member of the American Medical Association and the Kansas Medical Society; honorary member of the staffs of Bethany and Providence hospitals; at one time school principal; died June 1, aged 86, of coronary occlusion.

Perry, Malcolm Oliver, Allen, Texas; Fort Worth School of Medicine, Medical Department of Texas Christian University, 1917; died in Dallas May 27, aged 75, of acute myocardial infarction.

Phipps, Rufus Luther ✠ Clintwood, Va.; Louisville and Hospital Medical College, Louisville, Ky., 1908; served as vice president of the Medical Society of Virginia, president of the Clinch Valley Medical Society, and president of the Dickenson-Buchanan Counties Medical Society; medical advisor for the Selective Service in the county, and county coroner; physician in charge and owner of Dickenson County Hospital; died in the Medical College of Virginia, Hospital Division, Richmond, July 13, aged 69, of acute renal failure.

Renaker, John Gano, Covington, Ky.; Louisville (Ky.) Medical College, 1898; affiliated with St. Elizabeth Hospital; died May 30, aged 73, of heart disease.

Ruethin, Knute Albin ✠ Costa Mesa, Calif.; Bennett Medical College, Chicago, 1910; an Associate Fellow of the American Medical Association; member of the State Medical Society of Wisconsin; died in Hudson, Wis., June 13, aged 78, of coronary occlusion.

Schick, Frank Joseph ✠ Chicago; University of Illinois College of Medicine, Chicago, 1915; died in Kenora, Ont., Canada, July 2, aged 59, of heart disease.

Schoening, John Jacob, Philadelphia; Jefferson Medical College of Philadelphia, 1906; member of the American Medical Association; served with the division of medical services of the public schools; on the staff of the Stetson Hospital, where he died June 20, aged 66, of pulmonary embolus.

Scott, Lockburn Burton, Norfolk, Va.; Manitoba Medical College, Winnipeg, Man., Canada, 1907; member of the American Medical Association; for many years secretary-treasurer of the Norfolk County Medical Society; died May 17, aged 89, of arteriosclerosis.

Smith, Wiley J. S., Fouke, Ark. (licensed in Arkansas in 1903); died May 25, aged 93.

Sonnenburg, Willard Michael, Sheboygan, Wis.; Harvard Medical School, Boston, 1921; member of the American Medical Association; served as mayor of Sheboygan and as county physician; affiliated with St. Nicholas and Sheboygan Memorial hospitals; past president of the Sheboygan County Conservation Alliance; died March 13, aged 56, of acute myocardial infarction.

Tapper, George Washington, Monona, Iowa; State University of Iowa College of Medicine, Iowa City, 1896; died May 24, aged 81, of metastatic carcinoma.

Waller, Charles Edward, Troy, Kan.; Ensworth Medical College, St. Joseph, Mo., 1903; member of the American Medical Association; died in St. Joseph, Mo.; May 19, aged 72, of arteriosclerotic heart disease.

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GOVERNMENT SERVICES

AIR FORCE

New Base Medical Group Chief.—Maj. Irving L. Leff, formerly director of professional services in the Air Surgeon's office at Headquarters Central Air Defense Force, Kansas City, Mo., has been reassigned to Larson Air Force Base, Washington, where he will assume command of the Base Medical Group and be in charge of a 75-bed hospital. A rated Flight Surgeon, Major Leff is a graduate of the Medical Field Service School and the AAF School of Aviation Medicine.

Office of Surgeon General Moves to New Location.—The Office of the Surgeon General of the Air Force has moved from the Pentagon to Temporary Building No. 8, at 3800 Newark St., Northwest. The building is located in the northwest section of Washington, just off Wisconsin Avenue at the corner of 39th and Newark streets. The new telephone code number is 192 (ORdway 9600). Mail and telegraphic address remains the same as before: Headquarters, USAF, Washington 25, D. C.

Training in Survival.—How to live off the land in isolated mountain strongholds and arctic wastes was the subject of a recent talk at the Randolph Field School of Aviation Medicine by Maj. George R. Steinkamp, surgeon of the Strategic Air Command's survival school at Camp Carson, Colo. Major Steinkamp spoke to the current class of aviation medical examiners at the aeromedical school. Flyers in modern long-range bombers are likely to find themselves in wild and unfriendly places if they have to bail out or are forced down. To show them how they can maintain themselves in unfamiliar surroundings until rescuers reach them is the purpose of the survival school. Air crewmen at Camp Carson are taught survival procedures under conditions that closely simulate those of an actual emergency. Major Steinkamp exhibited to the student officers—some of whom may find themselves in B-36 squadrons later on—the special equipment which SAC researchers have designed to help airmen take care of themselves in the wilds. With these lightweight survival kits a downed crew member can build his own shelter, protect himself from icy winds or snow, and even bring down a passing moose for dinner.

ARMY

Neuropsychiatric Service Appointment.—Col. Charles S. Gersoni, MSC, has been named chief of the clinical psychology section of the neuropsychiatric service at Walter Reed Army Hospital. For the past four years, Colonel Gersoni has been the chief of the clinical psychology branch of the psychiatry and neurology consultants division of the Army Surgeon General's Office. He has been succeeded in the latter position by Lt. Col. Frederick A. Zehrer, MSC.

NAVY

Preventive Medicine.—Lt. (J.G.) Robert E. Mytinger, MSC, USN, of the preventive medicine division, will represent the Bureau of Medicine and Surgery, Aug. 20-27 at the National Convention of the National Association of Sanitarians, meeting at Miami Beach, Fla. Lieutenant Mytinger will present a paper on "Navy Training in Preventive Medicine."

Conference on Filariasis.—Lt. Leo A. Jachowski, MSC, USN, a parasitologist at the naval medical research unit of the National Naval Medical Center, Bethesda, Md., will represent the Navy at a conference of experts on filariasis and elephantiasis being held at Papeete, Tahiti, Aug. 20 to Sept. 3, 1951. The conference has been called by the South Pacific Commission on Filariasis and Elephantiasis, composed of members from the United Kingdom, France, Netherlands, New Zealand, Australia, and the United States, to discuss postwar research results that have not been published. The commission intends to compile all data for future publication.

Inspection Tour of Naval Medical Facilities.—Rear Adm. Lamont Pugh, Surgeon General of the Navy, returned Aug. 8 to Washington after a personal inspection tour of naval medical facilities in the Pacific Ocean area and the Far East including Korea. The Surgeon General found morale high among Navy medical department personnel and praised the readiness of the Navy medical facilities. Admiral Pugh said "procurement of blood and blood derivatives for use in Armed Forces medical installations still remains one of the outstanding major problems facing the country today." The use of whole blood and blood derivatives in continental Armed Forces hospitals for treatment of personnel of the Armed Forces, not necessarily Korean casualties, has not decreased. There has been a serious drain on existing stockpiles which require immediate replacement.

Rapid Mass Blood Count Method.—A new red blood cell counter that will greatly increase the speed of mass blood counts has been developed by Cornell University under an Office of Naval Research contract. Using the new instrument, which relates the red cell count to the electrical conductivity of whole blood, three technicians can perform 40 to 60 blood counts an hour by "production-line" methods, as compared to the present rate of about 12 to 18 an hour. Errors in the visual blood counting methods now used are avoided in the new instrument, since there is no dilution of the blood and the quantity used is not critical.

The counter was developed by Dr. I. S. Wright, Dr. Erwin Sheppard, and Professor W. C. Ballard Jr., of Cornell University, as part of a naval research study of the electrostatic forces in the blood and their relation to coagulation. Mass blood counts are vitally necessary under battle conditions in estimating damage due to hemorrhage, shock, flash burns, and exposure to ionizing radiations. The new method will also be helpful in making routine hospital blood counts and in screening men for military service.

VETERANS ADMINISTRATION

New Hospital Manager.—Dr. Leland E. Stillwell, chief of professional services at the Jefferson Barracks, Mo., Veterans Administration Hospital, has been appointed manager of the 500-bed VA hospital under construction at Iowa City, Iowa. Dr. Stillwell, a veteran of both World Wars, joined the VA Department of Medicine and Surgery in his present capacity in February, 1946.

Neurology and Psychiatry Residents.—Several openings are available in the residency training programs in neurology and in psychiatry at the Veterans Administration Hospital, Coatesville, Pa. The programs were organized by the Philadelphia Deans Committee. Both residencies cover a period of three years or less, depending on the previous experience of an applicant, and are designed to prepare residents for certification in neurology or psychiatry by the American Board of Psychiatry and Neurology. The programs include rotation through the Veterans Administration Hospital, Coatesville, Pa., Veterans Administration Mental Hygiene Clinic, Philadelphia, the Philadelphia General Hospital, and university and hospital outpatient clinics associated with Philadelphia's five medical schools. Applications should be sent to Vincent T. Lathbury, M.D., Executive Psychiatrist, Philadelphia Deans Committee, 111 N. 49th St., Philadelphia 39, Pa.

FOREIGN LETTERS

NORWAY

New Chairs of Medicine and Surgery.—In Oslo, the teaching of medical students has become increasingly dependent on institutions outside the old Rikshospital, particularly the Oslo City Hosptial, Ullevaal. In March, 1951, the title of professor was conferred on the heads of the chief departments at Ullevaal and on the head of the state asylum at Gaustad, Dr. Ørnulf Ødegaard. Dr. Ødegaard was born in 1901 and qualified as a doctor in 1925, becoming a doctor of medicine in 1933. He has been at the head of the Gaustad asylum since 1938. The promotion of Dr. C. A. Müller of Ullevaal to one of the new chairs of medicine comes comparatively late in life. He was born in 1886 and qualified as a doctor in 1910. Since 1928 he has been at the head of Department VIII of Ullevaal Hospital. Beloved by patients, students, and nurses, he also has an international reputation based on his work as a clinician and on his cardiovascular studies. The xanthomatosis and allied conditions described by him are known in the Scandinavian countries as Müller's disease.

Among the new professors is a younger man, Dr. H. J. Ustvedt who was born in 1903 and who is already well known abroad in connection with his work on tuberculosis and his participation in the International Tuberculosis Campaign. Since 1946 he has been at the head of Department IX of Ullevaal Hospital. Also on the medical side are the two new professors, Dr. R. T. Hatlehol, born in 1886, and Dr. P. M. Holst, born in 1892. On the surgical side there are two new professors, Dr. C. Rosing Bull, born in 1893, and Dr. C. B. Semb, born in 1895. Prof. Semb has been the chairman of the Norwegian Surgical Society since 1939. In May of this year he left Norway for Korea to supervise the Norwegian hospital there. Between 1945 and 1947 he was at the head of the Norwegian Army Medical Service. His contributions to the surgical treatment of pulmonary tuberculosis are familiar to many outside as well as inside the Scandinavian countries.

Sex Habits of Young Men.—Dr. Tore Berdal, of the Norwegian Army Medical Service, has undertaken a sort of Kinsey survey of the Norwegian soldiers who served in the army of occupation in Germany in 1949. A questionnaire was addressed to 2,750 privates and corporals, of whom 2,717 replied. The drafting of these answers was not compulsory, yet only about 1% of the recipients of the questionnaires left them blank. About 42% had had sexual intercourse during their six months' sojourn in Germany, and approximately one-third of the Norwegian forces in Germany must have had sexual intercourse with women more or less unknown to them. In Berdal's opinion this percentage is surprisingly high considering that fraternizing with the Germans was not permitted. The frequency of sexual intercourse was considerably lower (35.4%) among soldiers recruited from country districts in Norway than among soldiers from towns (58.4%). A comparison of the sexual intercourse rate among soldiers serving for six months at home and in Germany, respectively, showed little difference, 50.7% for Norway as compared with 43% for Germany.

Berdal's Table 7 deals with 1,621 soldiers who had not indulged in sexual intercourse throughout their sojourn in Germany and who gave their reasons for not doing so. Fear of venereal disease accounted for this in 23.6%, a permanent liaison at home for 19.7%, moral considerations for 9.4%, betrothal for 7%, marriage for 3.8%, religious considerations for 1.8%, various combinations of the above considerations for 31%, and other considerations for 3.6%.

Berdal's investigations also throw some light on condoms and their efficacy in preventing venereal disease. They were employed in 36% of a total of 8,470 sexual contacts made by 1,042 soldiers. In 543 cases the reasons that condoms were not employed were analyzed. In 59.3% the reason given was lack of a condom; in 14.4% it was considered unnecessary, as the women were supposed to be healthy, and in 7.5% it was dispensed with for ethical reasons, because it seemed unnatural. Other reasons that no condom was used were negligence due to alcohol, thoughtlessness, or the like. Berdal comments that as most of the women involved were strangers to the soldiers, it is remarkable that so few of them used condoms. He also quotes figures to show how effective condoms are in preventing venereal disease.

Completion of the International Tuberculosis Campaign.—Prof. H. J. Ustvedt, formerly deputy director of the International Tuberculosis Campaign, pointed out on June 30 that this date marked the completion of the International Tuberculosis Campaign. It was created in the winter of 1948 by the Danish and Swedish National Red Cross Societies, Norwegian Aid to Europe, and the United Nations International Children's Emergency Fund (UNICEF). This organization could provide dollars, and the Scandinavian organizations could supply expert personnel. The International Tuberculosis Campaign began its work in eight European countries to which teams were sent. Their activities spread to Asia, to North Africa, and, finally, to Latin America. The completion of the program, on June 30, 1951, does not mean that BCG vaccination has ceased on a large scale but that henceforth the World Health Organization has shouldered all the responsibility for this action with the continued economic support of UNICEF. While the International Tuberculosis Campaign was largely centralized in the Scandinavian countries, with headquarters in Copenhagen, the activities of the World Health Organization will be regional, with Geneva as the coordinating center.

With respect to the activities in the past three and a half years of the International Tuberculosis Campaign, Prof. Ustvedt pointed out that, though more than 38 million human beings have been tested with tuberculin and more than 17 million have been vaccinated with BCG, it is at present impossible to say to what extent this action has reduced the incidence of tuberculosis. A remarkable reduction in the incidence of tuberculous meningitis among children has been observed in certain European countries, and it may well be that this is the first observable outcome of BCG vaccination. Norway's contribution to this work has included 30 doctors and 46 nurses sent abroad with the BCG teams. Prof. Ustvedt concluded that these health missionaries to foreign countries are an admirable illustration of what small nations can do by peaceful means to promote world unification.

Norwegian Medical Film Archive.—Collection and distribution of educational medical films have not heretofore been centralized in Norway. Realizing the importance of this matter, Dr. Jens Björneboe, who edits the medical-scientific work of the organ of the Norwegian Medical Association, *Tidsskrift for Den Norske Laegeforening*, has lately taken an active part in negotiations which have now led to the centralization of these films in an organization known as the Norwegian Medical Film Archive. Among its sponsors are the Norwegian Medical Association, the Norwegian Ministry of Health, and the Faculty of Medicine. The new organization is affiliated with the Norwegian State Film Center, whose large staff of well-trained experts can be relied on to give invaluable aid to this new body. Hospitals and persons in the possession of medical films are invited to help this new body by loans and gifts. Gifts of medical films have already come from abroad, and it is hoped that the Norwegian Medical Film Archive will achieve its aim of acting as a center for lending educational films to all who can make proper use of them. The address is Norsk Medisinsk Filmarkiv, Statens Filmsentral, Kronprinsens gate 10 b. Oslo, Norway.

The items in these letters are contributed by regular correspondents in the various foreign countries.

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SWITZERLAND

Swiss Society for Internal Medicine.—The nineteenth annual meeting of the Swiss Society of Internal Medicine, under the chairmanship of Prof. P. H. Rossier (Zurich), was held in Coire June 1-3, 1951. These annual meetings are the main medical events of Switzerland. This year, the charming city of Coire, surrounded by mountains, welcomed over 250 specialists. Three principal interests were apparent: cardiology, hematology, and internal medicine.

The meeting of the cardiologists was attended by physicians from all parts of the country. Many foreign physicians had been invited, among them Dr. Frau (Milan), who opened the scientific session by showing the remarkable results of research on the dog concerning intraventricular conduction. Dr. Gilimann (Dusseldorf) presented an interesting study on the cardiac vectors.

From the hematologists came interesting reports on tapeworm anemia, the mechanism of which seems to have been made clear by Finnish authors. Prof. Heilmeyer, the German internist, drew attention to the use of cobalt in some anemias of the Cooley type, which do not respond to iron. The communication of Prof. Alder (Aarau, Switzerland) lessened the enthusiasm of those who thought of being able to count on effective treatment of leukemia; despite the great number of publications on this subject, transfusions are still the only effective supportive treatment of this disease. Even triethylenemelamine does not seem to give the results expected of it.

Prof. Rossier delivered a paper on relativity of numbers and of statistical methods in medicine. Prof. Hamburger (Paris) reported on the treatment of nephropathy. He discussed the osmotic and acid-base regulation of fluids and described two syndromes caused by hyperosmosis with cellular dehydration. Among the new treatments of nephritis, he discussed the intestinal perfusions undertaken in Paris.

The following day was devoted to arterial hypertension. In his report on medical treatment, Dr. J. J. Mozer (Geneva) warned against certain drugs which, given at the beginning of hospitalization, seem to have a hypotensive action, when mere rest can reduce the blood pressure and cause regression of eyeground changes.

Prof. Fontaine (Strasbourg, France) discussed the surgical treatment of arterial hypertension. He outlined the history of surgery of the sympathetic chain and of the adrenal gland. He favors subdiaphragmatic extirpation of the sympathetic system followed by unilateral adrenalectomy. Fontaine listed the indications for this operation. He pointed out that physicians and surgeons disagreed about the indications for this operation. There is no international classification of the different phases of hypertension. The value of the operation should not be judged according to the amount of hypertension before and after surgery. The patients who have undergone operation may be in perfect health even though their hypertension has been little modified. Prof. Rothlin (Bâle) emphasized the benefits of "hydergin" (ergot alkaloid mixture), which seems to be most effective when there are phenomena of autonomic dysfunction. Prof. Schoen (Gottingen, Germany) pointed out the value of physical therapy in the treatment of hypertension. Prof. Brunner and Dr. Dimtza opposed radical surgery and expressed the hope that it would soon be supplanted by medical treatment. Prof. Vannotti (Lausanne) agreed with Prof. Brunner and Dr. Dimtza.

ECUADOR

Mass Vaccination with BCG.—Mass vaccination is to be carried out throughout Ecuador. Up to now, more than 150,000 vaccinations given to children have resulted in negative reactions to the tuberculin test (Mantoux). The vaccination campaign is directed by Dr. Jorge A. Higgins of Ecuador. Swiss and North American doctors are also participating in the campaign.

CORRESPONDENCE

TOTAL POPULATION X-RAY SURVEYS

To the Editor:—THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION of July 7, 1951, carried an editorial on "The Value of Total Population X-Ray Surveys," which is based on reports of a study made in Gotland, an isolated Swedish island, and reported by Dr. L. Lonnerblad. This editorial, we believe, will be interpreted by many physicians as an indictment of community-wide chest x-ray surveys as they are being done in this country. It is our sincere hope that it was not the intention of the editorial staff to convey this impression.

After carefully studying this editorial and the original article published in *Acta Radiologica*, December, 1950, it is our considered impression that Dr. Lonnerblad, far from arguing the case against total population x-ray surveys alone, is presenting a case which in his experience is against the total tuberculosis control program as we know it in this country.

Very little of the text of Dr. Lonnerblad's article concerns itself with discussion of x-ray surveys, and the part of the article that is concerned with a critique of x-ray surveys is based on a photofluorography examination of the entire population of Gotland in 1943. Dr. Lonnerblad states: "Although the data from the photofluorography mass examination attempted on the entire population of Gotland made in 1943 *has not yet* been fully analyzed, it in a measure *seems* to confirm my hypotheses of 1942, viz., that a total population chest survey does not yield any conclusive results" (italics mine). While the article does state that 99% of the population were examined, no reference is made to other factors that have to do with the tuberculosis death rates, for instance, the type and extent of follow-up work, facilities for hospitalization and other forms of treatment, and the economic status of the population as it affects nutrition, housing, working conditions, and recreation. Certainly mass x-ray surveys cannot accomplish anything without the presence of these other factors; consequently, it is unfair to assume on this basis alone that x-ray surveys have no value.

It would seem to be a fair assumption that x-ray surveys are not a source of hindrance to the tuberculosis program. The only issue, therefore, is whether they are of any help. A priori, it must be admitted that one cannot consistently hit a mark unless he knows what he is shooting at, and where he is shooting. This is the sole purpose of x-ray surveys and would appear to be a self-evident aid to the tuberculosis control program. But, passing from the theoretical to practical experience, during the past five years in Florida over 1,700,000 persons have received x-ray survey examinations. Communities in this state have averaged a chest x-ray examination about once every 18 months instead of once in seven years, apparently as was the case in Gotland, since we do not have information to the contrary. The tuberculosis death rate has consistently declined, to an all-time low of 17 per 100,000 in Florida during the first five months of 1951. The fact that there appears to be any decline at all is most significant, since the rate has reached such low levels that it is now within the orbit of the law of diminishing returns. While no one is so naive as to assume that the x-ray surveys alone are responsible for the declining death rates, it would seem equally unsound to allege that x-ray surveys have not been an important factor.

Dr. Lonnerblad points out in his article that the death rate from tuberculosis in Gotland has not decreased appreciably over that in Sweden, but a table in the article by Dr. Lonnerblad certainly does not bear out this statement. In the year 1942 there were 0.96 deaths per thousand inhabitants in Gotland as against 0.68 deaths per thousand in Sweden as a whole. This had decreased to a point in 1947 where there were 0.49 deaths per thousand population in Gotland as against 0.48 deaths per thousand in Sweden as a whole. (Incidentally, the editorial in THE JOURNAL quoted this figure incorrectly, since it states the tuberculosis mortality rate for Gotland in 1946 was 0.54 per 100.)

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Dr. Lonnerblad in his discussion points out the inadequacy of our weapons in treating tuberculosis once the disease has been uncovered. He states: "Under existing conditions it would probably be necessary to intervene before the infection has taken place and thus accomplish what is done against other very frequent epidemic and endemic diseases, that is, perform mass inoculation in order to reduce the incidence of tuberculosis and thus avert the problems which naturally result. . . . It is not out of step to center our entire attention on the improvement of resistance of the entire population in a manner similar to that adopted for other very definite infectious diseases, e. g., typhoid fever. . . . With the advent of BCG vaccination we have at our disposal an additional agency of considerable protective value."

This, if I interpret Dr. Lonnerblad's article correctly, is the main thesis presented, and not an argument against x-ray surveys per se.

It is interesting that Dr. Lonnerblad mentions Dr. Arvid Wallgren in his discussion on the value of BCG. This same well-known author from Sweden stated: "On the other hand, one should not exaggerate the efficiency of BCG vaccinations. At best they may protect against the immediate consequence of virulent infection and diminish the incidence of primary and early post-primary tuberculosis. In my opinion, there is no prophylactic influence on the development of late manifestations of post-primary tuberculosis." (*Trans. National Association Prevention of Tuberculosis*, London, England, 1949.)

Certainly, in this country, where improved economic conditions, education, and rapidly expanding hospital facilities for isolation and treatment of active tuberculosis are combined with organized case-finding programs to insure the downward trend of the death rate, which is now the lowest on record, one could not advocate the general use of BCG.

After reviewing the editorial at issue and the abstract of the original article in THE JOURNAL, I am of the opinion that the main point of Dr. Lonnerblad's paper has been overlooked. In spite of the title of the article, it should be apparent to the reader that this paper represents a strong argument for the use of BCG in Gotland, rather than a criticism of the value of community-wide x-ray surveys.

C. M. SHARP, M.D., Director,
Bureau of Tuberculosis Control,
Jacksonville, Fla.

NERVE BLOCKING AND PAIN

To the Editor:—The June 30 issue of THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION contains a group of excellent papers, presenting results in various pain syndromes following block of the stellate ganglion, various nerves or infiltration of painful tissues. Although in some instances the results are remarkable, the authors were unable to explain the reason for the relief in many cases. For example, Adams, in his article "Diagnostic and Therapeutic Block" (page 803), recalled a patient "who had a small painful area in the chest wall" which affected his life considerably. "He had it for three years and was most discouraged. He did not appear to be neurotic, but this small area of pain was coloring his whole life. The cause of his pain was not obvious but for diagnosis, I blocked the area involved. He obtained immediate relief and was dismissed when he was pain-free for 48 hours. After three months he wrote me that his pain had not returned and that he could put in a comfortable day's work for the first time in three years.

"I do not yet know the origin or basis for this man's pain. The block therapy in his case was more or less a stab in the dark, but it produced results. In a neurotic patient who interprets even pressure as pain, this type of therapy would not have worked."

There is no doubt that definite relief of painful syndromes can be accomplished in many instances by successful nerve blocks; for example, trigeminal neuralgia, intracostal neuralgia, and pain secondary to fractured ribs and pleurisy. The literature is full of reports on excellent results following local and paravertebral block for painful syndromes, and in many of these cases the operator does not know the etiology of the pain. He is not sure of the position of his needles and may not have reached the ganglion or nerve with the injected material. Pender and Pugh (page 798 of the same issue of THE JOURNAL) have realized this difficulty and stress the use of roentgenograms to actually place and check the position of the needles.

I believe that those doing therapeutic nerve blocks for the relief of pain and other conditions would obtain a truer picture of the value of their procedure and also obtain a more accurate evaluation of the effect of "suggestion and the laying on of hands" if they would make it a rule to always precede the attempt at direct blocking by first trying a series of five to 10 intradermal wheels with sterile water placed at random in the skin area overlying the pain. Careful notes should then be made as to the relief of pain, if any, how soon it occurred, and how long it lasted. The results following this test, if unsuccessful or partially so, should then be compared with those following a definite attempt to block the nerve, ganglion, or tissue. I believe that such an approach to therapeutic nerve blocks would not only help to evaluate the patient with a hysterical or functional background but would also give the operator a better conception of what his procedure really accomplishes.

MICHAEL SCOTT, M.D.,
Temple University Hospital,
Broad and Ontario St., Philadelphia 40.

THE SURGEONS' FRONTIER

To the Editor:—Today's medical graduate faces the same problem that has confronted his predecessors: How shall he best develop his capacities and where shall he practice so as to best serve his patients and himself? Years ago young men were urged to go west and grow up with the country. Now the cities of the West are as crowded as those of the East. Where is today's frontier? For the surgeon the county seat town offers a challenge for his specialized services.

Staff appointment to the hospitals in these areas does not require certification by a board, but thorough training in general surgery is needed. These surgeons must be versatile. They must know their way around the abdomen and be competent to handle emergency situations in orthopedics, urology, and gynecology. They must be able to reduce fractures, use the cystoscope and perform cesarian sections. General surgery in the county seat town is all that the name implies. The surgeon is limited only by his ability and integrity in his efforts to save life.

Almost every county seat town in the country offers a place where a good surgeon is badly needed and where he can be successful if he knows how to properly utilize his knowledge. Communities where no other doctor is limiting his practice to general surgery present a golden opportunity. Naturally there will always be a number of general practitioners doing some surgery. The newcomer should not be discouraged if they do not welcome him with open arms. There will always be a few who will refer their surgical cases, and he will be able to win their confidence and through them gain a foothold. His acceptance will be easier if he discards whatever self-conceit he might have. It need not be beneath his dignity to assist an outside surgeon called in to operate, nor to help the family doctor in the postoperative care of this patient, without fee and without malice. He will be exploited at times almost beyond endurance, but humility will be rewarded as the years pass.

The first year will be difficult, for he may treat only a few patients and he may be tempted to fill in his time with general practice. There is nothing to be said against general practice, but no doctor can become a master surgeon and at the same time carry the load of a general practitioner. His time may better be used to survey the over-all medical needs of the community as a basis for future improvement. Any trade center with a population of 20,000 can eventually support a 50 to 100 bed hospital and two doctors specializing in general surgery. Thus he will do the community a real service if he later brings in an associate. This will allow time for study at other medical centers and still keep a surgeon in attendance. Good men attract good men, and gradually the community hospital will become a medical center.

GEORGE A. COLLETT, M.D., Elko, Nev.

MEDICAL MOTION PICTURES

The Steps of Age: Emotions of Everyday Living Series: 16 mm., black and white, sound, showing time 25 min. Produced in 1950 by Film Documents, New York, for the National Association for Mental Health, Inc., and the State of South Carolina. Procurable on purchase ($95) from International Film Bureau Inc., 6 North Michigan Ave., Chicago 2, or on loan from state or local mental health authorities.

This film is about a woman of 62, at the critical point, when she is crossing into the last quarter of her life. It shows her confusion and her first uneasy steps toward insight into herself and her problems. Treated very dramatically are the painful emotional problems engendered by her husband's having to retire from his job and the frustrations of unemployment due to old age. One of the most poignant scenes of the film deals with interpersonal relations among a grandmother, a mother, and a grandchild, where age differences contrive to turn love into hate.

Except for a few sequences, the approach of this film is negative; problems are presented, but few solutions are suggested. As such, it can be valuable when used with groups of young people to enable them to recognize and appreciate problems of which they may not be aware and as an introduction to a discussion of the positive means of solving these problems. Although a competent discussant should be present whenever this film is shown, the need for a discussant of exceptional ability must be recognized when the film is to be used with older people. It is highly recommended for social workers and graduate students of psychology and is also recommended for groups of young people and parent-teacher groups if competent discussion leaders are present. The photography, direction, and sound are excellent.

Gelfoam in Surgery: 16 mm., color, sound, showing time 25 min. Produced in 1949 for The Upjohn Company by Audio Productions Co., New York. Procurable on loan from The Upjohn Company, Kalamazoo, Mich.

This motion picture reveals a few of the elementary points about the clotting mechanisms of the blood as related to the use of hemostatic agents and clearly describes, without any unjust claims, the methods for using gelfoam* (absorbable gelatin sponge) in the control of hemorrhage. The process of its preparation is briefly described, and the picture demonstrates how it can be placed over the bleeding point as a small pack or patch to control hemorrhage and may be applied dry or moistened with saline. Originally it was thought that thrombin might be necessary, but it soon became obvious that it is needed only in unusual cases, such as hematopoietic diseases. Gelfoam® is absorbed by the tissues in about three weeks and produces a remarkably small amount of reaction as it is being absorbed. The picture depicts its use on the bleeding surface after cholecystectomy, prostatectomy, hemorrhoidectomy, and removal of brain tumors. The film recommends gelfoam® to fill in dead space; this use appears worthy of consideration. Its best application seems to be in control of hemorrhage following removal of brain tumors. Probably few surgeons will use it to control the bleeding following hemorrhoidectomy. Its dramatic use to stop bleeding from a puncture wound of the heart is described, but no claims are made for its use in this type of injury. This picture is recommended for a general surgical audience. The photography and narration are excellent, and the film is well organized.

Problems in the Treatment of Poliomyelitis: 16 mm., color, sound, showing time 40 min. Prepared in 1950 for The Division of Physical Medicine by Audio Visual Education Service, University of Minnesota, with the aid of a teaching grant from The National Foundation for Infantile Paralysis. Procurable on loan from The Division of Physical Medicine, University of Minnesota Medical School, Minneapolis.

This film shows, in a large series of patients, the effects of poliomyelitis on the various skeletal muscles of the body. The portrayal of actual situations and the presentation of theoretical considerations are not allowed to get between the object and the observer at any time. The involvement of individual muscles is well shown. In the beginning of the film, there are excellent demonstrations of the spasm of various muscles, in the sense that normal degrees of extension are shown to be painful. The extent of weakness and atrophy that can be produced is exhibited in the muscles of the legs, back, and arms, and in the diaphragm and other respiratory musculature. An extraordinary view is that of a boy in whom the infrahyoid and suprahyoid musculature becomes active because of the paralysis of the sternocleidomastoid muscles.

This motion picture would be of the highest educational value for anyone concerned with the detailed management of poliomyelitis. It is perhaps too long and too detailed for the average general practitioner, but it should be invaluable to the orthopedist, the specialist in physical medicine, and the physical therapist who follows through with the specific and detailed reeducation of the patient in whom paralysis follows an acute attack of poliomyelitis. The photography is good and the narration fair.

Problems of Rheumatoid Arthritis: 16 mm., color, sound, showing time 33 min. Produced in 1950 for The Arthritis and Rheumatism Foundation by Medical Film Guild, Ltd., New York. Procurable on loan or purchase from The Arthritis and Rheumatism Foundation, 535 Fifth Ave., New York.

This film reviews the incidence of arthritis, its economic and social significance, the lack of facilities for care, and the small sums available for medical research. The pathology, the clinical manifestations, and the treatment of rheumatoid arthritis are first presented, showing that arthritis therapy, long before cortisone and corticotrophin (ACTH) came along, had something to offer the patient, though largely nonspecific and preventive. There then follows a sequence on hormone therapy.

In general it is a good film. There seems to have been some confusion from the standpoint of intended audience. It is not technical enough for a medical audience and is too technical for lay groups. It is not made clear why rheumatoid arthritis is singled out. The problem of possible causation is dismissed much too early. It is recommended as an introductory film for medical students, nurses, and technicians. It might be of some value to lay audiences with some previous knowledge of this. This film is not recommended for specialists. The photography, animation, and narration are well done.

BUREAU OF LEGAL MEDICINE AND LEGISLATION

MEDICOLEGAL ABSTRACTS

Medical Practice Acts: Use of Injunction to Restrain Practice of Medicine by Chiropractor.—The State Board of Medical Registration and Examination filed suit to enjoin the defendant from practicing medicine without a license. From a judgment in favor of the defendant, the plaintiff appealed to the Supreme Court of Indiana.

Section 63—1311 of the Indiana Statutes provides that "to open an office for such purpose or to announce to the public in any way readiness to practice medicine in any county of the state, or to prescribe for, or to give surgical assistance to, or to heal, cure or relieve, or to attempt to heal, cure or relieve those suffering from injury or deformity, or disease of mind or body, or to advertise, or to announce to the public in any manner a readiness or ability to heal, cure or relieve those who may be suffering from injury or deformity, or disease of mind or body, shall be to engage in the practice of medicine within the meaning of this act. . . . It shall also be regarded as practicing medicine within the meaning of this act, if any one shall use in connection with his or her name, the words or letters, 'Dr.,' 'Doctor,' 'Professor,' 'M.D.,' or 'Healer,' or any other title, word, letter, or designation intending to imply or designate him or her as a practitioner of medicine or surgery in any of its branches." The same section also provides that in charging any person in a complaint for injunction, with a violation of this law by practicing medicine, surgery or obstetrics without a license, it shall be sufficient to charge that he did, upon a certain day and in a

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certain county, engage in the practice of medicine, he not having any license to do so, without averring any further or more particular facts concerning the same.

The defendant maintained an office with a reception room and treatment room in which there was an examination table, chairs, and the usual furniture found in the office of a professional man. Outside of the premises there was a sign with the lettering "R. W. Henry Chiropractor." The defendant had no license to practice chiropractic. On August 23, 1948, one of the dates charged in the complaint, a witness called at the office of the defendant for treatment, informed the defendant that he was suffering from headache and pains through his shoulder, and asked the defendant whether he could relieve him of these pains. The witness removed his shirt, at the defendant's request, and defendant ran his hands up and down his back and across his shoulders, explaining that the bone structure of a person's back and spine was such an intricate mechanism that he would not want to furnish any treatment until such time as x-rays proved there was cause for treatment, or the nature of the treatment needed. When he left the defendant's office, the witness took with him a pamphlet extolling the benefits of chiropractic treatment, at the bottom of page one of which was printed the words "R. W. Henry, D. C.," and at the bottom of the last page of which was the following: "R. W. Henry, D. C., Scientific Chiropractic, NCM and X-ray, Phone 4941, 1218 Kossuth Street, Lafayette, Indiana."

The clerk of the county court testified that he had the custody and care of the records relating to the issuance of licenses to practice medicine in any of its forms in the county, and that the defendant did not have either a drugless physician's or regular physician's license.

The only evidence produced by the defendant was a deposition of the secretary of the state board of medical registration and examination which stated, among other things, that a chiropractor can receive a license to practice in Indiana if he meets the same requirements as medical men; that there is no examination held exclusively for graduates of chiropractic colleges, whether such college is on the approved list or not; that an applicant would be admitted if he met the same requirements as would be required of a doctor of medicine; that a man, to take the examination, must be a graduate of an approved college; that as far as he knew there are no graduates of chiropractic colleges who have been permitted to take an examination conducted by the medical board since 1927; that the medical board is a composite board organized for the purpose of taking care of all systems of medicine.

The plaintiff contended that the undisputed and sole and only evidence introduced, revealed that the defendant was practicing medicine without a license and that the trial court abused its discretion in denying the plaintiff's request for an injunction. If the evidence is undisputed and uncontradicted that the defendant was practicing medicine without a license, said the Supreme Court, the trial court has no discretion but, as a matter of law, should grant a temporary injunction. Here the evidence showed that the defendant was practicing medicine within the meaning of the term as defined by the Indiana statutes.

The defendant contended, however, that since this was a case in equity, the State of Indiana was required to do equity; that the testimony of the secretary of the medical board showed that the board was administering the law in a discriminatory manner, and that therefore the state did not come into court with clean hands and was not entitled to injunctive relief. The Supreme Court pointed out, however, that the defendant failed to show that he himself had been injured, prejudiced or harmed by any action of the medical board. To avail the defendant, wrongful conduct on the part of the board must be proved to have affected the defendant himself. The defendant did not show that he had ever applied for examination or that the plaintiff had applied to him standards different from those fixed by the law and the duly adopted rules and regulations of the board. The Supreme Court therefore concluded that the evidence of the defendant was not sufficient to show that the plaintiff was not doing equity and did not come into court with clean hands.

Accordingly the Supreme Court found that the evidence was undisputed and uncontradicted that the defendant was practicing medicine without a license and that the trial court had no discretion but, as a matter of law, should have granted the temporary injunction. The judgment in favor of the defendant was reversed with instructions to grant the temporary injunction requested.—*State ex rel. Board of Medical Registration & Examination v. Henry, 97 N.E. (2d) 487 (Indiana 1951).*

Libel: Calling Chiropractic Advertising a Misrepresentation.—The plaintiff, Committee for Chiropractic Education Inc., a nonprofit corporation, filed suit against the State Medical Association of Texas and others for damages for publication of an alleged libel. From a judgment in favor of the plaintiff, the defendants appealed to the court of appeals of Texas.

The plaintiff is a nonprofit organization incorporated under the laws of the State of Texas for the purpose of maintaining a nonprofit educational foundation. In February, 1949, this organization caused to be published and circulated in Harris County and other counties in the State of Texas, eight pages of advertisements concerning the chiropractic profession. Some time later the State Medical Association of Texas, the Harris County Medical Society and the Travis County Medical Society joined in a statement which was published in a Houston, Texas, newspaper, which stated that the publication by the plaintiff in February "was a paid 'special edition' packed with misrepresentations. However, it was written to look like a real news section so that its misrepresentations might appear to be legitimate." The plaintiff alleged that it and the chiropractic profession in general had suffered great injury and damage from the publication and circulation of the defendants' statement and it sought recovery of actual and exemplary damages.

The defendant filed a plea of privilege and contended (1) that the plaintiff failed to make out a prima facie case of libel against it since the language charged as defamatory was in no sense libelous per se and (2) that the plaintiff's petition contained no specific charge of defamation, but merely charged that the defendant's statement alleged that the plaintiff's advertisement was "packed with misrepresentations."

In Roget's Thesaurus of English Words & Phrases, the word "misrepresentation" is classified as a "falsehood." The word "falsehood" is therein classified as being a misrepresentation; an untruth, and as perjury, false swearing, and fabrication. In Black's Law Dictionary, "misrepresentation" is defined as an untrue statement of fact, an incorrect or false representation which, if accepted, leads the mind to an apprehension of a condition other and different from that which exists. Webster's New International Dictionary defines "misrepresentation" as improper or unfaithful representation, and as false or incorrect statements, and as misrepresentations of a person's motives.

The courts of this state, said the court of appeal, have recognized that a misrepresentation is a falsehood or untruth with the intent and purpose of deceit. Whether the published statement complained of was a defamation and whether the statement was libelous per se are the controlling questions. It has been uniformly held that to impugn the veracity of a person is to defame him. It is also the established rule in this state that written or printed words which charge dishonesty or fraud, or rascality and general depravity are generally libelous per se. Article 5430 of the Texas statutes which defines libel, reads that "a libel is a defamation expressed in printing or writing . . . tending to injure the reputation of one who is alive, and thereby expose him to public hatred, contempt or ridicule, or financial injury, or to impeach the honesty, integrity, or virtue, or reputation of any one. . . ." We think it clear, said the Supreme Court of Texas in a prior case, that the enactment of the law, the purpose was not only to make definite what constitutes actionable libel in this state, but to materially modify the doctrine of the common law upon that subject. By the terms of the present law, a libelous publication, contrary to the common law rule, becomes actionable without the proof of malice, whether it is or not libelous per se. Under the present law the Supreme Court of Texas has held that it is not necessary to the right to maintain an action for a publication not libelous per se to allege or prove special damages. In this case, said the court of appeal, the trial court in effect found that the defendant's language was defamatory and libelous per se. Therefore the plaintiff was not required to prove special damages. The judgment overruling the defendants' plea of privilege was therefore affirmed.—*State Medical Association of Texas v. Committee for Chiropractic Education, 236 S.W. (2d) 632 (Texas 1951).*

MEDICAL LITERATURE ABSTRACTS

UNITED STATES

A.M.A. Arch. Internal Medicine, Chicago

87:775-900 (June) 1951

*Intravenous Use of Salt-Poor Human Albumin: Effects in 34 Patients with Decompensated Hepatic Cirrhosis. J. Post, J. V. Rose and S. M. Shore.—p. 775.
Effects of Veriloid* on Essential Hypertension: New Derivative of Veratrum Viride. A. L. Gropper, A. Surtshin and J. T. Hedrick. —p. 789.
Acute Benign Pericarditis. O. F. Rosenow and C. J. Cross.—p. 795.
*Benign Essential (Heredofamilial) Tremor. C. H. Davis Jr. and E. C. Kunkle.—p. 808.
Determination of Serum Protein-Bound Iodine as Routine Clinical Procedure. B. L. Hallman, P. K. Bondy and M. A. Hagewood.—p. 817.
Familial Leptocytosis (Cooley's Anemia and Cooley's Trait): Observations on Three Families, with Related Study of Bone Marrow Activity. H. E. Hamilton and W. M. Fowler.—p. 825.
*Terramycin in Treatment of Human Brucellosis. V. Knight, F. R. Sanchez and A. R. Sanchez.—p. 835.
Liver Cirrhosis: Relation Between Function and Structure Based on Biopsy Studies. S. S. Waldstein, H. Popper, P. B. Szanto and F. Steigmann.—p. 844.

Intravenously Administered Albumin in Cirrhosis.—Salt-poor human albumin was given intravenously to 34 patients critically ill with decompensated hepatic cirrhosis. The initial dose of 100 cc. of 25% solution twice daily was adjusted in each patient, so that a serum albumin level of 4.0 to 5.0 gm. was maintained. Treatment was continued for many weeks, the minimum effective total dose being about 625 gm. Diuresis, with clearing of ascites and edema, occurred in 21 patients. This was accompanied by an increase in appetite, weight, and strength and by a feeling of well-being. In most patients there was a decrease in jaundice. Of the 34 patients, 16 were in hepatic coma or semicoma when treatment was begun. Nine of these recovered, and eight had diuresis. The increased plasma volume and venous pressure associated with albumin therapy did not result in an increased incidence of bleeding from esophageal varices, but the authors warn that the patient's circulatory status must be carefully evaluated before albumin is given. They feel that salt-poor human albumin is a useful adjunct in the management of severely decompensated cirrhosis when adequate dietary therapy cannot be provided.

Benign Essential (Heredofamilial) Tremor.—This is a report of 14 cases of essential tremor encountered in a general hospital over 10 yr. From this series and from previous reports, the authors summarize the clinical features of this little-known but common hereditary disorder. The disease, which may begin at any period from infancy to old age, is characterized by a rhythmical tremor involving principally the hands, forearms, neck, head, and face. The tremor is generally decreased or absent at rest and present on voluntary increase in muscle tonus. It is aggravated by emotion, fatigue, cold, caffeine, and nicotine. Except for the increased terminal intention tremor, which may interfere with self-feeding and writing, accuracy and coordination are little involved. There are no defects in reflexes or in sensation. The tremor may progress for several years, remain stationary, and then progress rapidly again in old age. In most cases the disorder can be traced through several generations, frequently as a dominant characteristic. Both males and females are affected, and either sex may transmit the disease. The proper treatment of essential tremor is explanation and reassurance that the condition will not be disabling. Scopolamine hydrobromide and trihexyphenidyl have no significant therapeutic effect. Phenobarbital gives some symptomatic benefit, as does alcohol. The disease can be differentiated from Parkinsonism or progressive lenticular degeneration by the absence of rigidity, the preservation of automatic associated movements and rapid rhythmical alternating movements, the benign course, and the family history. It must be distinguished from tremors due to hyperthyroidism, cerebellar disease, dementia paralytica, and emotional tension. The underlying pathological lesion is not known.

Terramycin in Brucellosis.—Terramycin proved to be highly effective in the treatment of the acute manifestations of brucellosis in 11 patients, nine of whom were bacteremic. A 12th patient, with severe spondylitis as a complication of brucellosis, did not respond. The drug was given in a dose of 100 mg. per kilogram of body weight every six hours, or 150 mg. per kilogram every three hours, until defervescence, when the dose was reduced to 50 mg. per kilogram per day. Therapy was continued for 28 days. Striking relief of symptoms was noted within a few hours after the start of therapy, but bacteremia persisted for several days in some patients. Clinical and bacteriologic relapse occurred in two patients within three months. Both were successfully retreated with terramycin. All strains of Brucella tested were more sensitive in vitro to terramycin than to aureomycin or chloramphenicol, and therapeutic results were as good with terramycin as with the other two antibiotics. Results were far superior to those obtained with streptomycin and sulfadiazine. Animal experiments indicate that streptomycin enhances the effectiveness of terramycin against Brucella. This combination might reduce the rate of relapse. Further experiments demonstrated that smaller doses of terramycin (25 mg. per kilogram of body weight) also proved effective in the therapy of acute brucellosis.

A.M.A. Arch. Ophthalmology, Chicago

45:615-728 (June) 1951

Relation of Diplopia to Binocular Vision in Concomitant Strabismus. A. Posner and A. Schlossman.—p. 615.
*Ocular Complications Encountered in Intracranial Arteriography. H. F. Falls, R. C. Bassett and A. E. Lamberts.—p. 623.
Ophthalmoscopic Findings in Normal Premature Infants. G. S. Tyner. —p. 627.
Some Contemporary Concepts of Scleral Disease. K. C. Swan.—p. 630.
Cause of Failure in Retinal Detachment Surgery. P. R. McDonald. —p. 645.
Rate of Turnover of Ascorbic Acid in Aqueous Humor in Rabbits. B. Becker, E. Linner and E. Barany.—p. 653.
Aureomycin in Treatment of Trachoma. R. Ching.—p. 657.
Platinum Implant in Glaucoma Surgery. W. E. Muldoon, P. H. Ripple and H. C. Wilder.—p. 666.
New Plastic Surgical Drapes. T. S. Gerspacher, H. D. Fowler Jr. and D. E. Rolf.—p. 673.
Occlusion of Central Retinal Vein in Migraine. M. W. Friedman. —p. 678.
Optic Atrophy, Uveitis and Intracranial Disease. F. H. Adler.—p. 683.
Optics and Visual Physiology: Review of Literature for 1949 and 1950. K. N. Ogle.—p. 684.
Measurement of Visual Acuity: Critical Review. L. L. Sloan.—p. 704.

Ocular Complications in Intracranial Arteriography.—The frequency and type of ocular complications occurring after intracranial arteriography was investigated by the authors. A total of 80 consecutive patients undergoing this intervention were given an ophthalmologic examination before and after the angiographic examination. A table listing the petechial hemorrhages observed shows that 35 patients had cutaneous, 65 conjunctival, and 20 retinal petechial hemorrhages. More than half the patients had petechiae in two or three of these locations. Pupillary dilatation, optic neuritis, angiospasm of retinal vessels, and blindness were also observed. The cause of these complications is not known, but they undoubtedly result from vascular changes secondary to allergic, toxic, or physical phenomena.

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An asterisk (*) before a title indicates that the article is abstracted.

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A.M.A. Arch. Pathology, Chicago

51:567-670 (June) 1951

Morphology of Sporotrichum Schenckii and Histoplasma Capsulatum in Tissue. A. M. Kligman and G. D. Baldridge.—p. 567.
Hypertensive Cardiovascular Disease: Vascular Lesions of Dogs Maintained for Extended Periods Following Bilateral Nephrectomy or Ureteral Ligation. E. E. Muirhead, L. B. Turner and A. Grollman. —p. 575.
In Vitro Effects of Cortisone on Mesodermal Tissue. G. D. Baldridge, A. M. Kligman, M. J. Lipnik and D. M. Pillsbury.—p. 593.
Serum Glycoproteins in Experimental Scurvy. C. L. Pirani and H. R. Catchpole.—p. 597.
Attempts to Produce Rheumatic Carditis in Laboratory Animals by Means of Streptococcic Injury. J. J. Robinson.—p. 602.
Experimental Cholesterol Arteriosclerosis: III. Reaction of White Blood Cells. R. Altschul and M. E. Martin.—p. 617.
*Botulism, Complication of Clostridium Botulinum Wound Infection. C. G. Thomas Jr., M. F. Keleher and A. P. McKee.—p. 623.
Localization of Nephrotoxic Antigen Within Isolated Renal Glomerulus. C. A. Krakower and S. A. Greenspon.—p. 629.

Clostridium Botulinum Infection of a Wound.—Although a few cases have been reported in which Clostridium botulinum was isolated from traumatic wounds, in none of these were symptoms of botulism present. This paper reports the case of a boy, 13, who died of botulism following contamination with Cl. botulinum of a relatively minor gunshot wound of the thigh. He had rapidly progressive generalized muscular weakness and great prostration, associated with dysphagia, dysphonia, and inability to cough. Death, which occurred nine days after the injury, was due to respiratory failure and bilateral lobular pneumonia. It would seem that botulism from this source might occur more frequently, since the organism is ubiquitous in nature, a potential contaminant of every traumatic wound. Furthermore, its growth requirements for initiating an infection appear to be almost identical with those of Cl. tetani. Finally, botulism has been produced in experimental animals by the injection of heated spores, and investigators have demonstrated that the botulinus toxin may be absorbed from broken skin and fresh wounds. The observations in this case were consistent with the findings in botulism, except for severe cerebral edema, which has not been previously reported, but which may actually have been a consequence of respiratory failure and cerebral hypoxia.

American J. Digestive Diseases, Fort Wayne, Ind.

18:145-174 (May) 1951

Effect of ACTH in Case of Beta Islet Cell Adenoma of Pancreas. G. M. Brown.—p. 145.
Gastrointestinal Syndrome of Reducible Hernia. H. Gauss.—p. 146.
The "Bolen Test" in Diagnosis of Neoplasms. A. C. Nickel, R. Berger and P. Brickley.—p. 150.
Modern Concepts in Treatment of Fistula in Ano. G. L. Becker.—p. 152.
Streptococci, Diplostreptococci and Respective Filtrable Agents from Outdoor Air During Epidemics of Respiratory Infections and Infectious Gastroenteritis. E. C. Rosenow.—p. 155.
Responses of Guinea Pig's Ileum to Histamine, Acetylcholine, Antigen, and Electrical Stimulation as Influenced by Progressive Decreases in Concentrations of Calcium, Magnesium, or Potassium Separately or in Pairs. B. N. Craver and W. E. Barrett.—p. 163.
*Fatal Gastric Hemorrhage Following Aureomycin. W. P. Kleitsch. —p. 166.
Bowel Perforation Due to Ingested Foreign Bodies. W. P. Kleitsch and G. S. Sinow.—p. 167.

Fatal Gastric Hemorrhage Following Aureomycin.—Kleitsch reports the case of a man who was given aureomycin in 250 mg. doses every four hours when a recurrent bronchopleural fistula failed to respond to penicillin therapy. Aureomycin was discontinued after 20 days of consecutive administration. Several days later the patient had a severe gastric hemorrhage, which was followed by death. Necropsy revealed that it was caused by hemorrhage from a large ulcer 3 cm. in diameter in the pyloric antrum immediately adjacent to the duodenum. Before aureomycin therapy there had been roentgenographic evidence of a small ulcer in this region. It is not possible to state unequivocally that the fatal hemorrhage in this case was due to aureomycin therapy. This patient's poor general condition contributed to his rapid death. Loss of appetite and a diminished intake of food probably favored extension of his peptic ulcer. However, one may be justified in assuming that aureomycin played at least a contributory role. Aureomycin in solution has an acid reaction and it seems likely that the continuous administration of such an acid solution to a patient with a peptic ulcer might aggravate the ulceration.

American Journal of Medicine, New York

10:671-792 (June) 1951

*Prophylaxis of Acute Rheumatic Fever by Treatment of Preceding Streptococcal Infection with Various Amounts of Depot Penicillin. L. W. Wannamaker, C. H. Rammelkamp Jr., F. W. Denny and others. —p. 673.
*Chloramphenicol in Treatment of Meningococcal Meningitis. F. R. McCrumb, H. E. Hall, A. M. Merideth and others.—p. 696.
Evaluation of Hemagglutination Test for Tuberculosis. J. W. Fleming, E. H. Runyon and M. M. Cummings.—p. 704.
Behavior of Myocardium in Health and Disease as Studied by Coronary Sinus Catheterization. R. J. Bing and R. Daley.—p. 711.
Influence of Chronic Pulmonary Disease on Heart and Circulation. R. M. Harvey, M. I. Ferrer, D. W. Richards Jr. and A. Cournand.—p. 719.

Prophylaxis of Acute Rheumatic Fever.—Procaine penicillin G in oil containing 2% aluminum monostearate was injected intramuscularly according to one of three dosage schedules in 1,178 patients with exudative tonsillitis or pharyngitis in an attempt to prevent the development of acute rheumatic fever in these patients, while 1,162 patients were untreated and served as controls. Of the 1,178 patients, 634 were given a total dose of 1,200,000 units of penicillin in three injections over a period of 96 hr., 254 were given 600,000 units in two injections over 72 hr., and 290 were given a single injection of 600,000 units. In 10 patients who had received penicillin and in 42 patients who received no treatment rheumatic fever or possible rheumatic fever developed following the observed illness. Data collected on the rheumatic patients in both the treated and untreated groups showed that when the time interval between the onset of exudative tonsillitis or pharyngitis and the onset of rheumatic fever was prolonged, there was bacteriologic or serologic evidence, or evidence from the history, of an intervening untreated streptococcic infection in many instances. This is in contrast to the almost complete lack of such evidence of a second infection in cases in which the interval was short. If one excludes those cases of rheumatic fever developing after a 45 day interval between the two diseases, there were two cases of rheumatic fever in the treated group and 28 in the control patients. These data indicate that penicillin treatment of acute streptococcic infections almost completely prevents the subsequent occurrence of acute rheumatic fever. Penicillin treatment was also observed to eradicate the streptococci from the oropharynx of the majority of persons and to inhibit the formation of antistreptolysin. The most pronounced inhibition of antibody was that obtained by the dosage schedule of three injections of penicillin over a 96 hr. period totaling 1,200,000 units of the antibiotic.

Chloramphenicol in Meningitis.—Preliminary tests for in vitro sensitivity of six strains of Neisseria intracellularis to chloramphenicol (chloromycetin®) confirmed the observation made by others that chloramphenicol is significantly active against N. intracellularis. Animal experiments showed that a high level of protection is afforded by chloramphenicol in mice infected with N. intracellularis. Fifteen patients, 12 children and three adults, with meningococcic meningitis were treated with chloramphenicol. Children received approximately 0.25 gm. orally at four hour intervals (1.5 gm. daily) and adults 1 gm. every eight hours (3 gm. daily) after a large initial dose based on 50 mg. per kilogram of body weight. In five instances chloramphenicol was administered intravenously in the early stages of treatment to achieve a high concentration of antibiotic in the blood and cerebrospinal fluid. The total amount of chloramphenicol administered to the 15 patients varied from 5.5 to 30 gm., given over a mean period of 5.6 days. In no instance was treatment continued longer than nine and a half days. Adequate concentrations were observed in the blood and spinal fluid in patients receiving the drug either intravenously or orally. Specimens of spinal fluid initially positive for meningococci in all patients became sterile within 36 hr. after the institution of specific therapy. During the first 48 hr. of therapy an elevation rather than a depression of the spinal fluid white cell count occurred in most of the patients, but meningococci were usually absent as determined by culture. Clearing of the spinal fluid occurred with surprising rapidity. Temperatures were restored to normal on an average of three and a half days. In six instances during the convalescent period, sporadic elevations of temperature were noted but were not indicative of relapse. There was remarkable

improvement in the appearance of the patients within the first 24 hr. of treatment. After the third day convalescence proceeded uneventfully. One patient with fulminant meningococcemia and meningitis responded very favorably to chloramphenicol. The results in these 15 patients indicate that chloramphenicol is an effective weapon against meningococcic meningitis. There were no fatalities, nor were there residual signs of meningitis, except in one patient, who showed ophthalmoplegia before antibiotic treatment was instituted. This eventually cleared.

American J. Obstetrics and Gynecology, St. Louis

61:953-1192 (May) 1951. **Partial Index**

*Pathogenesis and Relationship of Hyaline-Like Pulmonary Membrane to Premature Neonatal Mortality. P. D. Bruns and L. V. Shields.—p. 953.
Carcinoma of Corpus Uteri in Young Women. M. B. Dockerty, S. B. Lovelady and G. T. Foust Jr.—p. 966.
Anticoagulant Therapy in Gynecologic Surgery. B. E. Urdan and M. Wagner.—p. 982.
Hormone Secretion by Human Placenta Grown in Eyes of Rabbits. H. L. Stewart Jr.—p. 990.
Toleration of High Water Intake by Patients with High-Grade Mitral Stenosis in Last Trimester of Pregnancy. W. W. Hurst and F. L. McPhail.—p. 1001.
Surgical Management of Bleeding of Late Pregnancy. Z. J. R. Hollenbeck and J. H. Williams.—p. 1012.
Male Factor in Sterility. C. O. McCormick Jr.—p. 1020.
Oxygen Studies of Arterial Blood in Newborn Infants. J. Watts, H. Henderson, D. H. Kaump and R. M. Davis.—p. 1025.
Bilateral Polycystic Ovaries, Stein-Syndrome. M. L. Leventhal and M. R. Cohen.—p. 1034.
Malignant Myoblastoma Vulvae. W. P. Sadler and M. B. Dockerty.—p. 1047.
Diagonal Conjugate. D. F. Kaltreider.—p. 1075.
Clinical Evaluation of Use of Methylergonovine Tartrate (Methergine) with Calcium Gluconogalactogluconate (Neo-Calglucon) Following Third Stage of Labor. H. V. Sandin and J. A. Hardy.—p. 1087.
Diabetes in Pregnancy. R. E. Hall and A. J. B. Tillman.—p. 1107.
Cause of Blood Coagulation Defect Following Abruptio Placentae. E. W. Page, L. D. Fulton and M. B. Glendening.—p. 1116.
Acute Appendicitis Incidental to Gynecologic Abdominal Procedures. E. M. Rosset and A. S. Conston.—p. 1136.
Serum Thiocyanate Levels in Pregnancy. D. D. Deeds and P. B. Donovan.—p. 1146.
Use of Blood Serum in Male Frog Test for Pregnancy. A. L. Haskins and A. I. Sherman.—p. 1150.
*Study of 475 Pregnancies in American Indian Women. C. S. McCammon.—p. 1159.

Hyaline-Like Pulmonary Membrane in Premature Neonatal Mortality.—A pulmonary hyaline membrane is found at autopsy in a significant number of premature babies. This hyaline-like membrane has been described under such terms as asphyxial membrane, aspiration pneumonia, hyaline membrane, congenital pneumonia, vernix membrane, desquamative anaerosis, eosinophilic membrane, fibrinoid exudate or necrosis, and congenital alveolar dysplasia. This study is based on necropsies performed on 439 infants who died neonatally and 264 stillborn infants, making a total of 703, among which were found 114 cases with hyaline-like pulmonary membrane (16.4%). The highest incidence occurred in the birth weight category of 1,000 to 1,500 gm. Maternal and infant histories, which were available for only 62 of the 114 infants with this membrane, are analyzed, and experiments on animals are described. The authors think that the membrane is probably not related to the aspiration of the contents of the amniotic sac. Prematurity was the only apparent predisposing factor to formation of the membrane in the lungs of these infants who died in the neonatal period. When there is a triad of (*a*) a clinical history of an uncomplicated premature birth, (*b*) progressive respiratory embarrassment with death in one to five days, and (*c*) the presence of the hyaline-like membrane as the only significant autopsy finding, the case can be recognized as hyaline-like membrane disease. Injury from intrauterine anoxia and extrauterine therapy with high concentration of oxygen (over 60%) may be involved in the formation of the membrane in premature infants. Further clinical and laboratory studies are necessary to determine the effects of oxygen concentration, barometric pressure, and humidity on respiration of premature infants.

Pregnancy in American Indian Women.—Observations were made on 475 pregnant American Indian women who were delivered at the Navaho Medical Center over the 26 month period ending in August, 1950. These women came to the hospital by choice. Nausea and vomiting related to pregnancy occurred in only 14% of these women. Only 30 patients gave histories of previous miscarriage. A total of 57 cases of threatened, incomplete, and completed abortions were seen during this study. There were two women with eclampsia and 23 with severe preeclampsia. There were no maternal deaths, but there were three neonatal deaths. Of the systemic diseases complicating pregnancy, syphilis was the most prevalent, with an incidence of 6.9%. However, there were only two fetal deaths attributed to untreated maternal syphilis. Cesarean section was thought to be indicated in only eight patients. High forceps and extraction were never used. The average age for the 100 primiparas was 20.5 years. There were six women 16 years old or younger, the youngest being 13. There were four primiparas 30 years old or older, the oldest being 32. Of the 475 women, 33 were 40 or older, and 75 had had eight or more pregnancies. One group of women had no fear of labor; the other group feared labor and needed analgesia and anesthesia. Almost all of the first group were unable to speak English and had had little contact with the white race and its customs. Only eight cases of uterine carcinoma were diagnosed among 6,685 hospital admissions during the period of this study possibly because of unusual vaginal cleanliness in these women. Congenital anomalies occurred in eight infants.

American Journal of Ophthalmology, Chicago

34:1-208 (May) (Part II) 1951. **Partial Index**

Trachoma-Psittacosis-Lymphogranuloma Venereum Group of Viruses: Chlamydozoaceae. P. Thygeson.—p. 7.
*Visual Illusions in Night Flying. H. A. Imus, A. Graybiel, R. H. Brown and J. I. Niven.—p. 35.
Flicker Fusion Fields: IV. Neuro-Ophthalmic Lesions. P. W. Miles.—p. 51.
Further Considerations of Fixation Disparity and Binocular Fusional Processes. K. N. Ogle and A. deH. Prangen.—p. 57.
Effect of ACTH and Cortisone on Ocular Disease. M. J. Hogan, E. P. Engelman, P. Thygeson and M. Krupp.—p. 73.
Relation of Steroid Hormones to Development of Experimental Exophthalmos. G. K. Smelser and V. Ozanics.—p. 87.
Study on Penetration of Cysteine and Cystine into Aqueous Humor of Rabbits and Its Relation to Early X-Irradiation Effects on Eye. L. von Sallmann, Z. Dische, G. Ehrlich and C. M. Munoz.—p. 95.
Studies on Oxidation of Cysteine to Cystine in Lens Proteins During Cataract Formation. Z. Dische and H. Zil.—p. 104.
Aqueous:Plasma Steady-State Ratios: Their Variations and Significance. J. E. Harris and L. B. Gehrsitz.—p. 113.
Further Studies on Cholinesterase Activity in Ocular Tissues. A. de Roetth Jr.—p. 120.
Inhibition by Thiamine Chloride on Retinal Responses Caused by Nicotine. A. I. Fink.—p. 139.
Influence of Donor-Recipient Sensitization on Corneal Grafts. A. E. Maumenee.—p. 142.
Aureomycin, Chloromycetin, and Terramycin in Experimental Herpes-Simplex Virus Infections. H. O. Geller and P. Thygeson.—p. 165.
Separation of Pars Ciliaris Retinae in Retrolental Fibroplasia. J. M. Dixon and E. V. Paul.—p. 182.

Visual Illusions In Flying.—Unusual airfcraft accidents led to experiments on visual illusions that affect pilots in operating aircraft at night or under adverse conditions of visibility and weather. A survey of aviators indicated that such illusions were relatively frequent. Experiments revealed that flying hazards are increased by illusions to which all pilots are susceptible. Autokinetic illusions can occur in night flying but can be controlled if the number of formation lights on the planes is increased and if pilots are instructed to shift their gaze. Experiments in a Bárány chair, a rotating Link trainer, and the human centrifuge indicated that acceleration and deceleration forces produce illusions of motion and displacement of visual targets and illusions of changes in bodily position. Repeated experiments, both in the laboratory and in flight, show that the illusions persist, and that the subjects do not become adapted to the illusory effects. A pilot, when flying at night or in a fog, cannot tell whether he is in a climbing turn or in a diving turn. Pilots must rely on instruments and must learn to ignore their bodily sensations, no matter how overpowering they may be. Much of the fear and mystery involved in spatial disorientation are removed when pilots understand the cause of these illusions and how to counteract them.

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American Journal of Pathology, Ann Arbor, Mich.

27:349-536 (May-June) 1951

Generalized Hypertrophic Osteoarthropathy: Pathologic Study of Seven Cases. E. A. Gall, G. A. Bennett and W. Bauer.—p. 349.
Metastasizing Carcinoma of Parathyroid Gland with Osteitis Fibrosa Cystica and Extensive Calcinosis. J. T. Ellis and D. P. Barr.—p. 383.
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Thrombosis of Renal Veins with Massive Hemorrhagic Infarction of Kidneys in Childhood: Report of Four Cases. S. D. Kobernick, J. R. Moore and F. W. Wiglesworth.—p. 435.
Electron Microscope Studies of Collagen from Normal and Diseased Tissues. J. C. Gale.—p. 455.
*Histopathology and Etiology of Pneumonia in Children Dying After Antibacterial Therapy. M. L. Menten and G. A. McCloskey.—p. 477.
Localized Tuberculoid Granulomas Associated with Carcinoma: Their Relationship to Sarcoidosis. W. St. Symmers.—p. 493.
Malignant Melanoma in the Tropics. W. F. Enos and R. H. Holmes. —p. 523.

Pneumonia After Antibacterial Therapy.—Since the introduction of sulfonamides and antibiotics into the therapeutic management of pneumonia, death from bacterial infections of the respiratory tract now rarely occurs in adults, and in children fatalities have been greatly reduced. With penicillin therapy, the temperature usually fell to normal within 24 hr. and improvement in the clinical condition was noted. Hospitalization ranged from two to five days. Fatal cases were limited generally to infants 2 or 3 weeks old or to children with some additional disease. In the past 10 yr. Menten and McCloskey examined lungs from approximately 250 children who died from pneumonia and from about 450 other children who died from different causes but who also had complicating terminal pneumonia. Lungs of children dying with pneumonia after receiving adequate antibiotic treatment contained few or no bacteria. These abacterial lungs showed extensive cellular hyperplasia of the alveolar walls and few or no neutrophilic leukocytes. The bronchi and bronchioles were free from involvement and appeared normal. Whether the tissue changes were caused by residual toxins of bacteria removed from the field by sulfonamides and antibiotics or were due to an unidentified virus remains unanswered.

Am. J. Syphilis, Gonorrhea and Ven. Dis., St. Louis

35:201-300 (May) 1951

Studies on Treponemes of Bejel: I. History, Morphologic Characteristics, and Staining Properties. E. Rizk, G. Garabedian, H. Chaglassian and A. Pipkin.—p. 201.
Id.: II. Transmission to Rabbits and Observations on Course of Experimental Infection. E. Rizk, E. Shwayri and G. Garabedian.—p. 207.
Studies on Life Cycle of Spirochetes: VII. Life Cycle of Kazan Nonpathogenic Treponema Pallidum in Culture. E. D. DeLamater, M. Haanes and R. H. Wiggall.—p. 216.
Reports of North Carolina Syphilis Studies: V. Indices in Measurement of Congenital Syphilis. J. J. Wright, C. G. Sheps and A. E. Gifford. —p. 225.
*Chloromycetin (Chloramphenicol) in Treatment of Various Types of Syphilis: Preliminary Report. M. J. Romansky, S. Olansky, S. R. Taggart and others.—p. 234.
Total Dosage Factor in Use of Crystalline Penicillin G: Treatment of Early Syphilis. F. Plotke, J. Rodriquez and G. X. Schwemlein. —p. 240.
*One-Injection Schedule for Treatment of Early Syphilis. J. Rodriquez, G. X. Schwemlein and F. Plotke.—p. 246.
Penicillin Therapy of Cardiovascular Syphilis with Large Total Dosage: Its Rationale Based on Histologic Studies. W. L. Bruetsch.—p. 252.
Occurrence of Jarisch-Herxheimer Reaction in Patient with Gummatous Syphilitic Aortitis. C. M. Whorton and S. W. Denham.—p. 255.
Saccular Aneurysm of Aorta in 32-Year-Old Man with Persistently Negative Serologic Tests. A. Kahn Jr. and M. J. Kilbury.—p. 263.
Homologous Serum Hepatitis Complicating Therapeutic Malaria for Neurosyphilis. H. Koteen, C. A. Kane and M. Rosenberg.—p. 270.
Clinical Follow-Up Studies on 130 Cases of Long-Standing Paretic Neurosyphilis Treated with Penicillin. A. S. Rose and L. R. Carmen. —p. 278.
Involvement of Stomach in Early Syphilis, "Precocious Tertiarism": Report of Case. C. D. Bell.—p. 284.
Simple Stain for Donovan Bodies for Diagnosis of Granuloma Inguinale. R. B. Greenblatt, R. B. Dienst and R. M. West.—p. 291.
Nine Cases of Granuloma Inguinale Treated with Chloromycetin. M. Zises and G. C. Smith.—p. 294.

Chloramphenicol in Syphilis.—This study concerns a clinical and serologic evaluation of syphilitic patients treated with varying dosages of chloramphenicol. The daily dose was divided into six portions and administered orally every four hours. The dosages were established on the basis of weight groups rather than the exact weight of each patient. Seventy-nine patients with primary and secondary syphilis were treated with 30 and 60 mg. per kilogram of body weight daily for four to eight days. The initial results in clinical healing of primary and secondary lesions were as favorable as with penicillin treatment. The highest percentage of seronegativity was achieved by patients treated with 60 mg. per kilogram daily for eight days. Dryness of the mouth and mild diarrhea occurred only occasionally. Several patients had mild Jarisch-Herxheimer reactions manifested by 1 to 2 degrees (F.) elevation of temperature. Red granular glossitis and pharyngitis developed in five patients, but the tongue and pharynx rapidly returned to normal following the administration of vitamin B complex. The serologic progress of all except one of the 11 patients with early latent syphilis was favorable; but within the short period of the follow-up, none attained seronegativity. Ulcerative lesions healed in all three patients with late syphilis who were treated with 60 mg. per kilogram daily for 15 days. The cerebrospinal fluid cell counts of a patient with paresis and of two with acute meningovascular syphilis returned to normal after 15 days' treatment. No improvement was noted in a patient with optic atrophy and a patient with tabes dorsalis. As regards the possible masking effect on a syphilitic infection when small doses of chloramphenicol are used to treat gonorrhea, the authors believe that the same post-treatment observation for the possible development of concomitantly acquired syphilis should be observed as has been advised following penicillin treatment, i. e., from four to six months. Chloramphenicol appears to be an effective oral antisyphilitic agent. In the treatment of neurosyphilis, this antibiotic should be given for at least 15 days.

One-Injection Schedule for Early Syphilis.—Procaine penicillin G, by providing adequate, sustained penicillin blood levels, led to the investigation of the single dose schedule in the treatment of syphilis. Seventy-one patients with dark-field positive syphilis were treated. In 36 patients a diagnosis of secondary syphilis was made; 21 patients were seropositive primary, and 14 were seronegative primary. To each of the 71 patients 2,400,000 units of crystalline procaine penicillin G in peanut oil with 2% aluminum monostearate was given intramuscularly in injections of 600,000 units at each of four sites simultaneously. At the end of a follow-up period of six or seven months, 70% of the patients were clinically and serologically negative. No serious reactions were observed. Effective blood levels were maintained for all the patients for 96 hr. following the one-injection schedule. Preliminary results of this study indicate that a one-injection schedule is effective in the treatment of early syphilis; however, longer periods of observation are necessary for final evaluation.

American Journal of Tropical Medicine, Baltimore

31:275-410 (May) 1951. **Partial Index**

Laboratory and Clinical Observations on Effect of Terramycin in Treatment of Amebiasis. H. Most and F. van Assendelft.—p. 284.
Malaria Control in Southern Territory of Lower California. W. G. Downs, E. Bordas and M. Correa Colorado.—p. 286.
Comparative Effects of Certain Species of Trypanosomidae on Growth of Endamoeba Histolytica in Absence of Bacteria. V. P. Phillips.—p. 290.
Evaluation of Efficiency of Common Cotton Rat Ectoparasites in Transmission of Murine Typhus. C. B. Worth and E. R. Rickard.—295.
Transient Presence of Complement-Fixing Antibodies Against Murine Typhus Fever in Sera of Offspring of Immune Rats. C. B. Worth. —p. 299.
Transmission of Murine Typhus in Roof Rats in Absence of Ectoparasites. C. B. Worth and E. R. Rickard.—p. 301.
Survival Time of Rickettsias of Murine Typhus in Infected Flea Feces. E. R. Rickard.—p. 306.
Effect of Chloromycetin on Experimental S. Typhosa Infection in Rabbits. O. M. Gruhzit and R. A. Fisken.—p. 329.
Blood and Bone Marrow Pattern in Sleeping Sickness in Portuguese Guinea. C. Trincão and E. de Gouveia.—p. 335.
Observations on Cases of Schistosomiasis Mansoni in Non-Endemic Area (Aruba, N. W. I.). A. Le Poole.—p. 346.
Entomological Background of Distribution of Murine Typhus and Murine Plague in the United States. C. O. Mohr.—p. 355.
Laboratory and Field Studies on Biology of Relapsing Fever Tick Vector (Ornithodoros Hermsi Wheeler) in High Mountains of California. D. S. Longanecker.—p. 373.

American Surgeon, Atlanta, Ga.

5:371-470 (May) 1951

Traumatic Diaphragmatic Hernia: Case Report. B. W. Ward.—p. 371.
Spleen, Few Surgical Aspects. D. P. Hall.—p. 376.
Obstruction of Gastroenterostomy Stoma Due to Thrombosis of Omentum. V. L. Rees and V. M. Pond.—p. 391.
*External Endometriosis, Clinical and Experimental. R. W. Te Linde and R. B. Scott.—p. 397.
Thyroid Crisis. J. D. Rives and R. M. Shepard.—p. 406.
Cross Finger Flap: New Method of Repair. T. D. Cronin.—p. 419.
Colostomy and Ileostomy. W. C. Cantey and G. T. McCutchen.—p. 426.
Carcinoma of Cervix in Pregnancy. W. E. Brown and G. C. Jernigan.—p. 441.
Importance of Histologic Examination of Miniature Pathologic Lesions: Brief Discussion of 15 Illustrative Cases. F. C. Helwig.—p. 448.
Mesenteric Vascular Occlusion and Duodenal Infarction: With Report of Unusual Case. J. L. Duer and T. O. Hodges.—p. 455.

External Endometriosis.—Te Linde and Scott limit their discussion to external endometriosis, pointing out that internal endometriosis or adenomyosis is a separate clinical entity. External endometriosis is increasing, and it occurs oftenest in women in the childbearing age. The authors review their observations on 243 women in whom they performed operations primarily for endometriosis. Pain in the lower abdomen and especially dysmenorrhea are the most characteristic symptoms. There is, however, no typical history of endometriosis, and the authors feel that laparotomy on the basis of the history alone is not justifiable. If surgical treatment is used in young women it should be conservative, so that the woman will still be able to bear children. The evidence concerning the value of hormones is still inadequate. The authors use hormones only for patients who refuse surgical treatment. Because testosterone has been known to cause hirsutism, they prefer diethylstilbestrol, but this hormone has been known to produce severe uterine hemorrhage. Various theories have been advanced with regard to the etiology of endometriosis. The authors feel that their experiments on the creation of endometriosis in the monkey indicate that cast-off menstrual endometrium is capable of growth. This fact greatly strengthens Sampson's theory of retrograde menstruation.

Annals of Internal Medicine, Lancaster, Pa.

34:1093-1310 (May) 1951

Present Status of Etiology of Pernicious Anemia. W. B. Castle.—p. 1093.
*Treatment of Angina Pectoris with Propylthiouracil. L. Waitzkin.—p. 1107.
Association of Nodular Goiter with Thoracic Pain: Report of Seven Cases. E. Rose and J. Edeiken.—p. 1126.
Relation of Hyperplastic Arteriosclerosis to Diabetes Mellitus. E. Moschcowitz.—p. 1137.
Chronic Trench Foot: Study of 100 Cases. W. Redisch, O. Brandman and S. Rainone.—p. 1163.
Tuberculous Pericarditis: Report of Three Cases Treated with Streptomycin. R. P. Natelson.—p. 1169.
Liver Function Tests in Nonspecific Arthritis with Special Reference to Hyperglobulinemia. B. H. Archer.—p. 1173.
Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Review of Literature and Report of Case. J. D. Hallahan and T. Klein.—p. 1179.
Interstitial Gastric Emphysema Following Gastroscopy: Its Relation to Syndrome of Pneumoperitoneum and Generalized Emphysema with Evident Perforation. S. M. Fierst, H. M. Robinson and L. Lasagna.—p. 1202.
Sarcoidosis: V. Effects of Pregnancy on Course of Disease. S. W. Donaldson, A. C. Tompsett, R. H. Grekin and A. C. Curtis.—p. 1213.
Purpura as Manifestation of Penicillin Sensitivity. L. H. Criep and S. G. Cohen.—p. 1219.
Arthritis Due to Intestinal Amebiasis. E. M. Rappaport, A. X. Rossien and L. A. Rosenblum.—p. 1224.
*Treatment of Pneumonia with Bacitracin. E. H. Reisner Jr., F. N. Bailey and E. Appelbaum.—p. 1232.
*Lipedema of Legs: Syndrome Characterized by Fat Legs and Edema. L. E. Wold, E. A. Hines Jr. and E. V. Allen.—p. 1243.

Treatment of Angina Pectoris with Propylthiouracil.—Thyroidectomy has been largely abandoned as a treatment for angina pectoris, but the antithyroid drugs have been employed by some investigators. This paper reports on seven patients treated with propylthiouracil who had had angina pectoris for over a year but no recent attacks of myocardial infarction or congestive failure. Coronary arteriosclerosis was the only apparent cause of angina pectoris. Relief of pain was significant in three of the seven patients, transient in one, slight in one, and absent in two. When benefit occurred, it usually appeared about two months after the beginning of treatment with propylthiouracil. Mild to moderate myxedema was produced in all cases. No toxic reactions were encountered, even with large doses (800 to 3,000 mg. daily) for many months. Improvement may be related to a decline of the circulating thyroid hormone rather than to general metabolic depression. The results seem sufficiently favorable for this therapy to be considered in cases in which the usual medical measures fail to restore a reasonable degree of painless activity. Before the therapy is abandoned as ineffective, dosage should be adjusted and treatment continued until myxedema becomes evident.

Treatment of Pneumonia with Bacitracin.—Bacitracin is an antibiotic produced by the Tracy I strain of Bacillus subtilis. Its bactericidal spectrum is comparable to that of penicillin in local as well as systemic application, and it is sometimes effective when other treatments fail. Reisner and associates tried bacitracin in lobar pneumonia because pneumococci are highly sensitive to bacitracin, and because pneumonia runs a sufficiently consistent course to permit the evaluation of a new therapy. Bacitracin in doses of 15,000 units every six hours intramuscularly cured early cases of pneumonia without bacteremia, but such doses were inadequate to clear the blood of infection. Of eight patients treated with the small doses, five recovered and three had to be changed to penicillin therapy to effect cure. In a later study 14 patients with lobar pneumonia were treated with bacitracin in doses of 30,000 to 99,000 units intramuscularly every six hours. Twelve of these 14 patients recovered, one had to be changed to penicillin therapy, and one died of bacterial endocarditis, although his pneumonia responded well to treatment. The authors feel that bacitracin is an effective agent in the treatment of pneumococcic pneumonia. All patients had moderate albuminuria, casts, and impairment of concentrative power of the kidney and of phenolsulfonphthalein excretion, lasting for a variable time after therapy. This nephrotoxicity of bacitracin necessitates caution but does not contraindicate its use in suitable cases.

Lipedema of Legs.—Wold and associates present observations on 119 cases of lipedema, which were examined at the Mayo Clinic from 1937 through 1946. The term lipedema was coined by two of the authors to describe large legs due to the subcutaneous deposition of fat in the buttocks and lower extremities and the accumulation of fluid in the legs. Characteristically, there is symmetrical bilateral enlargement of the buttocks and lower extremities, which begins almost imperceptibly and progresses gradually. Progressive enlargement of the limbs is ordinarily associated with gain of weight, but evidence of obesity of the trunk, upper extremities, face, and neck may be entirely absent. The enlargement of the limbs is accentuated by orthostatic activity, particularly in warm weather, and, although rest in bed may cause some decrease in size of the limbs, owing to removal of fluid, even prolonged bed rest will not reduce the limbs to normal size. The authors stress that this condition differs from lymphedema in that women are almost exclusively affected, that both limbs are symmetrically involved, that the swelling is usually soft and that pitting is minimal, that there is usually a family history of large legs, and that episodes of inflammation, such as are commonly observed in lymphedema, are usually absent. Each of the 119 patients observed at the Mayo Clinic was examined by one of the consultants in the section on peripheral vascular disease, since the disease is often confused with chronic venous insufficiency and lymphedema. All but one of the patients were women. Most of the patients were overweight, a preponderance of the excess fat being in the lower half of the body. In most instances this represented an exaggeration of the normal female configuration. Discomfort in the legs, consisting of diffuse pain, tenderness, and aching distress, was a prominent symptom in about one-half of the group. Chronic induration cellulitis and stasis lesions did not occur unless there was an associated, coincidental chronic venous insufficiency. The basal metabolic rate was usually less than 0%, but none of the group had clinical evidence of myxedema. Anxiety concerning the appearance of the lower extremities and possible serious significance of the edema was usual.

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California Medicine, San Francisco

74:365-412 (May) 1951

Carcinoma of Thyroid Gland. R. S. Pollack.—p. 365.
The Collagen Diseases. H. R. Fisher.—p. 371.
Management of Cancer of Nasal Cavity and Paranasal Sinuses. S. L. Perzik.—p. 374.
Hysterical Abdominal Distention Simulating Acute Intestinal Obstruction: With Report of Case. P. R. Westdahl.—p. 377.
Evaluation of Subjective Complaints in Relation to Disability Claims. W. I. Nesson and P. Thurber Jr.—p. 381.
Precipitation of Clinical Poliomyelitis by Injections. L. S. Goerke. —p. 383.
Legal Duties of Physicians. A. A. Sandor.—p. 385.

Cancer Research, Chicago

11:393-480 (June) 1951. **Partial Index**

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Steroid Hormones and Tumor-Host Relations. R. W. Begg.—p. 406.
Pathogenesis of Uterine Lesions in Virgin Mice and in Gonadectomized Mice Bearing Adrenal Cortical and Pituitary Tumors. N. P. Christy, M. M. Dickie, W. B. Atkinson and G. W. Woolley.—p. 413.
Carcinogenic Derivatives of Fluorene Containing Isotopic Nitrogen. M. F. Argus and F. E. Ray.—p. 423.
Use of Serum Proteins in Measuring Activity of Prostatic Cancer. C. Huggins and R. Baker.—p. 428.
Effect of Complete Ablation of Thyroid Tissue by Radioactive Iodine on Survival of Tumor-Bearing Mice. H. A. Sloviter.
Development of Mammary Cancer in Castrate A Strain Male Mice Bearing Ovarian Grafts. R. A. Huseby and J. J. Bittner.—p. 450.
Study of Tryptophan-Acid and Iodoacetate Index Tests in Patients with Malignancy. C. Riegel, R. Jones, K. J. Welch and J. Valentine. —p. 453.
Regeneration of Liver in Parabiotic Rats. N. L. R. Bucher, J. F. Scott and J. C. Aub.—p. 457.
Transformation of Solid Transplantable Mouse Carcinoma into "Ascites Tumor." G. Klein and E. Klein.—p. 466.

Geriatrics, Minneapolis

6:143-204 (May-June) 1951

Geriatrics and Rehabilitation. H. A. Rusk.—p. 143.
Psychological Investigation of Senile Dementia. H. Dörken and V. A. Kral.—p. 151.
*Variations in Electrocardiogram Changes in Emotional State. I. Stevenson, C. H. Duncan and H. S. Ripley.—p. 164.
Chronic Arthritis of Senescence. R. L. Cecil.—p. 179.
Studies in Atherosclerosis: VI. Albumin as Stabilizer of Cholesterol Sols. O. J. Pollak.—p. 182.

Electrocardiographic Changes During Emotion.—A group of 35 patients, including 18 men and 17 women about half of whom were over 45 years of age, were subjected to electrocardiographic tests. The majority had complaints referable to the cardiovascular system, some originating in structural heart disease, others in purely functional disturbances. Electrocardiographic electrodes were attached to the patient, who lay on a bed while he was interviewed. The physician, who was familiar with the patient's history, directed the conversation from time to time to topics known to be disturbing to the patient and which were relevant to his illness. At other times the patient was asked to relax or was diverted by pleasant conversation. Electrocardiograms were taken at frequent intervals during the interview. Notes were made of the patient's behavior, movements, voice, and remarks, as an aid to the assessment of his emotional state. In order to compare the electrocardiographic changes coincident to the stress of life situations with those resulting from another type of stress the electrocardiograms after exercise were studied in 19 of the patients. In five of these 19, the rate after exercise did not reach that during anxiety in the interview. In one of these the heart rate during emotional disturbance was 112 and immediately after exercise (the equivalent of walking briskly up four flights of stairs) did not exceed 95. In 14 patients the rate immediately after exercise was comparable to that attained during the emotional disturbance, so that the electrocardiographic complexes could be compared at similar heart rates. In eight of these the electrocardiogram was identical following exercise and during the disturbed emotional state. In four others the changes were in a similar direction but less in degree after exercise than during anxiety or resentment. In the remaining two the changes after exercise and during anxiety were in a different direction.

Illinois Medical Journal, Chicago

99:281-326 (June) 1951

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The State of Illinois Cooperates with the Ophthalmologist and Otolaryngologist. H. R. Kobes.—p. 303.
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Pernicious Anemia in the Negro. E. Coffman, M. Slavin and W. G. Hartnett.—p. 313.
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Emphysema of Gallbladder. J. P. Doenges and B. A. Weber.—p. 319.

International Journal of Leprosy, New Orleans

19:1-116 (Jan.-March) 1951

*Status of Streptomycin and Dihydrostreptomycin in Treatment of Leprosy. P. T. Erickson.—p. 1.
Sundry Experiences in Chemotherapy of Leprosy. J. Lowe.—p. 15.
Lucio's Spotted Leprosy (Diffuse Lepromatous Leprosy of Mexico): Report of Case in Hawaii. H. L. Arnold Jr. and N. R. Sloan.—p. 23.
Incomplete Alternating Bipolar Form of Leprosy: Atypical Case. J. Gomez Orbaneja and J. R. Puchol.—p. 29.
*Sudden Appearance of Lepromatous Eruption During Prolonged Administration of Stilbestrol in Case of Unsuspected Leprosy. W. St. C. Symmers.—p. 37.
Tuberculin Reaction in Patients of Fiji Leprosy Hospital. C. J. Austin. —p. 45.
Serial Cephalin Flocculation Test in Leprosy: Preliminary Report. Sister Hilary Ross.—p. 51.
Wolbach and Schaumann Type Inclusions in Giant Cells in Leprosy: Probable Value in Prognosis. O. C. Croxatto and J. Chiriboga.—p. 59.

Streptomycin in Leprosy.—Observations on 114 patients with leprosy revealed that in doses as low as 0.5 gm. daily, streptomycin and dihydrostreptomycin favorably influence the specific cutaneous and mucous membrane lesions. The symptoms associated with acute or recurrent iridocylitis can often be controlled with these antibiotics, but they exert little, if any, beneficial effect on such complications as acute lymphadenitis, orchitis, neuritis, or the associated edema of the mucous membranes or skin. The appearance of toxic manifestations, vertigo, tinnitus, and loss of hearing usually precludes the continuous administration of streptomycin or dihydrostreptomycin beyond a period of six months, and rarely will a patient tolerate them for more than a year. Although there is much clinical improvement at the end of such periods of treatment, the concentration of bacilli in the remaining skin lesions remains unaltered. However, reduction in size of lepromas must represent a reduction in the absolute number of bacilli in the tissue. The results obtained with these antibiotics resemble those obtained with the sulfones, but these can be administered indefinitely, and with them a reduction of bacilli in nodular lepromatous lesions can be demonstrated after two or three years of treatment. The early response of mucous membrane lesions to the antibiotics is undoubtedly due to the elimination of secondary invaders, growing in and upon leprous lesions of the nasal, pharyngeal, and laryngeal mucous membranes. However, the healing of the leprous ulcerations indicates that the antibiotics also influence these lesions themselves. Unless less toxic products are found, or unless the dosage can be further reduced without impairing the therapeutic activity, streptomycin and dihydrostreptomycin can be used only as adjuvants to sulfone therapy. They can be used (1) in combination with the sulfones to hasten resolution of specific leprous skin and mucous membrane lesions at the beginning of treatment; (2) to effect further clearing of residual leprous skin lesions that have reached a stationary stage with sulfone treatment; (3) to relieve annoying symptoms of sulfone-resistant mucous membrane lesions and to heal such lesions; (4) to abort attacks of acute leprous iridocyclitis; and (5) for treatment of patients who have an idiosyncrasy to the sulfones.

Lepromatous Eruption During Diethylstilbestrol Therapy.—In a man, 84, a widespread lepromatous eruption on the limbs and erythema of the chest developed in the course of a few days. There were no other signs of leprosy, and he had no constitutional symptoms. Thirteen months before the skin eruption appeared, prostatic carcinoma had been diagnosed clinically; oral treatment with diethylstilbestrol (α,α'-diethyl-4,4'-stilbene-

diol) was started at that time and was continued until the skin lesions appeared. Even when the prostate was first examined rectally, it was felt that the findings on palpation were not so characteristic of carcinoma as to exclude a purely inflammatory condition. As there were no grounds for surgical intervention, and as, in view of the patient's age, biopsy was not considered essential, no histological examination was made. In the light of the leprous nature of the skin lesions, it may be that the patient actually had lepromatous prostatitis and osteitis. Whether there was any relation between the prolonged and heavy dosage with a powerful synthetic estrogen and the sudden clinical manifestation of a hitherto unsuspected infection by Mycobacterium leprae may interest leprologists, since hormone preparations are used in patients with leprosy for intercurrent conditions. It also raises the question whether hormones might be useful adjuvants to other therapy in leprosy. It is possible that the predominantly male sex incidence of leprosy during the reproductive years of life is in part determined by hormones. The puerperal exacerbations of leprosy suggests that conditions prevail at this time that favor an acceleration of the infection, and these conditions may be related to the change in endocrine balance then obtaining. The literature reveals a case of a woman in whom leprosy appeared during treatment with thyroid.

Journal of Allergy, St. Louis

22:195-290 (May) 1951

*ACTH and Cortisone in Allergic Manifestations: Therapeutic Results and Studies on Immunological and Tissue Reactivity. S. M. Feinberg, T. B. Dannenberg and S. Malkiel.—p. 195.
*ACTH and Cortisone in Allergic Diseases: Clinical, Serologic (Electrophoretic), and Immunologic Studies. R. A. Cooke, W. B. Sherman, A. E. O. Menzel and others.—p. 211.
Cutaneous Reactions to Staphylococcus Polysaccharide, Protein, and Unfractionated Extract in Hypersensitive and Normal Individuals. M. C. Kahn, H. S. Baldwin, B. R. Zeitlin and M. Smart.—p. 237.
Electrocardiographic Changes in Experimental Anaphylactic Reactions. G. Mikulicich.—p. 249.
Absence of Nonspecific Anamnestic Stimulation of Antistreptolysin in Pneumococcus Pneumonia. C. Y. Sugihara and T. L. Squier.—p. 264.
Allergic Reaction to Aureomycin with Demonstration of Positive Skin Test to Serum Containing Aureomycin. E. B. Brown and M. Goodgold.—p. 273.

ACTH and Cortisone in Allergic Manifestations.—Fifteen patients with severe and intractable asthma of four months' to 54 years' duration were treated with corticotrophin (ACTH) and/or cortisone. Corticotrophin was administered four times daily, usually in 20 mg. doses, for four to 29 days. For most patients the total dose for the course was about 400 to 500 mg., although in three it was over 1,000 mg. If the response was satisfactory, the doses were gradually reduced, beginning about the fourth to the fifth day. If the response was considered unsatisfactory, cortisone was added, while administration of corticotrophin was continued or reduced. Several patients were given cortisone from the start. The daily dose in such cases was 200 mg. in two injections per day for the first two or three days, reduced subsequently to 100 mg. Six patients obtained complete relief, all of them with corticotrophin. Incomplete yet satisfactory relief was obtained in four, two of these with corticotrophin, one with cortisone, and one with corticotrophin followed by cortisone. Associated nasal symptoms also improved, but less rapidly and less pronouncedly than the asthma. In five patients results were slight or questionable. After treatment was stopped, relapses occurred in most of the patients. Seven additional patients were treated with corticotrophin or cortisone for syndromes other than asthma; one had generalized and weeping atopic dermatitis, two had severe generalized reactions to penicillin administration, one had generalized eczematoid dermatitis, and three had hay fever. Satisfactory results were obtained in the patients with dermatitis and penicillin reactions, while moderate symptoms were not definitely removed in the patients with hay fever. Corticotrophin and cortisone are of appreciable value in the temporary treatment of certain types and phases of allergic syndromes. They are most helpful in intractable asthma, in acute status asthmaticus, and in severe drug reactions. Limitations in the usefulness of these hormones are as follows: 1. The length of remissions after a single course of treatment varies from a few days to a few months. 2. The necessity for frequent injections is a handicap. 3. Some types of allergy do not respond. Corticotrophin and cortisone are not substitutes for more basic allergic management. The dangers and hazards from continuous and sometimes from temporary use of these drugs are numerous, and the hormones must not be employed without a full understanding of their many actions. In patients treated with corticotrophin or cortisone the skin reactions to antigens and histamine remained unchanged. Quantitative studies of the ophthalmic and nasal reactions in those who had nasal and conjunctival allergy showed them not to be significantly altered. Sensitizing antibodies remained unaffected after treatment with corticotrophin or cortisone. It is possible that the simple titration tests do not simulate the conditions of chronic allergy and that tests devised to resemble more closely continuous allergic stimulation might show a more decisive influence of these hormones on allergic reactivity.

Corticotrophin and Cortisone in Allergic Diseases.—Thirty-one patients with persistent severe asthma that was of bacteria. or combined bacterial-inhalant origin were treated with cortisone or corticotrophin. In adults the daily dosage was rarely over 100 mg. for cortisone or 80 mg. for corticotrophin in divided doses at six hour intervals. With children and infants the doses were one-half or less of the adult dose. Occasionally, a patient was comfortably free of dyspnea by the third day, but in severe cases recovery took from 10 to 14 days. In almost all cases relief of dyspnea eventually was substantial, but asthma returned within a few days or weeks after cessation of treatment. Eleven additional patients, six adults and five infants with allergic dermatitis, were treated with corticotrophin and cortisone. The dosage and the results were the same as in the patients with asthma. Five patients with chronic urticaria of many months' duration obtained relief in three to five days with corticotrophin or cortisone, but there was little lasting effect unless a cause was discovered and removed. The value of a temporary respite must not be minimized, and the benefits of prolonged treatment with corticotrophin and cortisone have not yet been adequately explored. Chemical and electrophoretic studies were made on the serums of 19 adult patients with chronic infective asthma, five adult patients with chronic intrinsic dermatitis, and four children with intrinsic dermatitis (infantile eczema). The patterns in many serums showed distinctly abnormal distribution of the various protein fractions, albumin, and alpha$_1$, alpha$_2$, beta, and gamma globulins. Comparative studies suggested that these changes are not the result of the allergic state per se, but are related directly or indirectly to the chronic underlying infection, since similar alterations of protein distribution have been observed in such chronic nonallergic infections as osteomyelitis and bronchiectasis. These changes were even comparable to the profound changes recorded by Reiner in lupus erythematosus. Immunologic studies indicated that the symptomatic benefits and tissue alterations resulting from treatment with corticotrophin and cortisone are not due to interference with the immediate wheal type reaction of antigen-antibody sensitized cells. It was further observed that the skin-sensitizing antibody of allergic serums is not wholly contained in the gamma globulin fraction of such serums.

J. Pharmacology & Exper. Therap., Baltimore

102:1-70 (May) 1951

Relationship Between Cholinesterase Activity and Brain Permeability. M. E. Greig and T. C. Mayberry.—p. 1.
Physiological Disposition and Cardiac Effects of Procaine Amide. L. C. Mark, H. J. Kayden, J. M. Steele and others.—p. 5.
Alkyl Nitrites: XIV. Effect of Nitrites and Nitrates on Arterial Adenosine Triphosphatase. J. C. Krantz Jr., C. J. Carr and H. H. Bryant.—p. 16.
Action on Nicotine-Induced Tremors of Substances Effective in Parkinsonism. D. Bovet and V. G. Lango.—p. 22.
Factors Influencing Fluoroacetate Poisoning: Practical Treatment with Glycerol Monoacetate. M. B. Chenoweth, A. Kandel, L. B. Johnson and D. R. Bennett.—p. 31.
Effect of Topically Applied Adrenergic Blocking Agents upon Peripheral Vascular System. T. J. Haley and M. Andem.—p. 50.
Physiological Performance Following Hypnotic Dose of Barbiturate. R. E. Goodnow, H. K. Beecher, M. A. B. Brazier and others.—p. 55.
Metabolic Effects of Anesthesia: II. Comparison of Acid-Base Equilibrium in Man and in Dogs During Ether and During Cyclopropane Anesthesia. J. P. Bunker, H. K. Beecher, B. D. Briggs and others.—p. 62.

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Missouri State Medical Assn. Journal, St. Louis

48:349-420 (May) 1951

Primary Suture of Colostomies. R. J. Crider and B. L. Neubeiser. —p. 365.
Role of Edema in Clinical Gynecology. G. L. Miller.—p. 367.

48:421-492 (June) 1951

Fractures About the Ankle. R. L. Diveley.—p. 437.
Prevention of Suicide. J. R. Eidelman.—p. 441.
Disseminated Lupus Erythematosus in Identical Twin Sisters Associated with Diabetes Mellitus in One Case. M. W. Davis and G. H. Gutridge.—p. 446.

New England Journal of Medicine, Boston

244:743-776 (May 17) 1951

*Acute Myocardial Infarction: Ten-Year Study. G. E. MacDonald and W. B. A. Bentley.—p. 743.
Epidemic Diarrhea of Unknown Cause: Report of Outbreaks in Three Massachusetts State Hospitals. S. A. Britten, A. D. Rubenstein, N. Raskin and G. Strassmann.—p. 749.
*Reaction of Adrenal Cortex to Physical and Emotional Stress in College Oarsmen. A. E. Renold, T. B. Quigley, H. E. Kennard and G. W. Thorn.—p. 754.
Genital Dermatitis Caused by Penicillin: Its Response to Nicotinic Acid. G. E. Morris.—p. 758.
Medicine as a Science: Psychiatry. E. Lindemann.—p. 759.

Acute Myocardial Infarction.—The authors discuss data obtained from clinical records and gross or microscopic postmortem observations in 100 cases of acute myocardial infarction that occurred in 60 men and 40 women between 1940 and 1949. Without the aid of the electrocardiogram, the clinical diagnosis of myocardial infarction was made correctly in 69 cases. Electrocardiograms were taken in 85 cases. Microscopic dating at autopsy indicated that the infarction occurred prior to the taking of the electrocardiogram in 75 cases. An electrocardiographic diagnosis of recent infarction was made in only 52 (69%) of these. Reevaluation of the electrocardiogram in an additional six instances (8%) revealed patterns strongly suggestive of acute infarcts; in two instances a "residual" coronary pattern was present. In only 11 cases no changes suggestive of myocardial infarction were noted. In 72 of the 85 cases the three standard limb leads with one precordial lead (CF_4) were employed initially. In 62 of these infarction had occurred prior to the last electrocardiogram. Although there was electrocardiographic evidence of acute infarction in only 45 (72%) of these, an additional nine cases (14%) showed abnormal changes compatible with possible infarction. Thus in 86% of cases in which only these four leads were used the presence of acute infarction was either indicated or suggested. The anterior wall of the left ventricle was involved in 68 instances, the lateral wall in 23, the posterior portion of the left ventricle in 30, the posterior right ventricle in one, the anterior portion of the interventricular septum in 22, and the posterior septum in six. There were eight cases of rupture of the ventricle. A close correlation was observed between the clinical and microscopic estimates of the age of an infarct, when Mallory's criteria were used. The commonest associated major pathological conditions were pronounced generalized arteriosclerosis in 50 cases, chronic cholecystitis with cholelithiasis in 13 cases, and pulmonary infarcts in nine cases.

Reaction of Adrenal Cortex to Stress.—Adrenal cortex response to standardized physical exertion and added emotional stress, as measured by changes in circulating eosinophil levels, was studied in healthy, well-trained oarsmen. Members of the Harvard varsity and combination crews were observed during a two-week training period and immediately before and after contests with Yale crews. In the varsity crew, within four hours of the first time trial, the original average eosinophil level of 123 was reduced to 19 and after the second time trial to 38. Immediately before the actual race the average count was only 64 and fell to 3 within four hours thereafter. In certain oarsmen the lowest level of circulating eosinophils was reached after one hour, whereas in most it was reached only after four hours. It should be emphasized that the varsity four-mile race was extremely hard and tense, won by only a quarter of a length, with a spectacular and frightening finish. In the combination crew, after the time trial the average initial count of 108 fell to a final 56. On the day of the actual race the initial count was low, averaging 42 and there was no fall at either one or four hours; there was a slight mean rise to 59 eosinophils per cubic millimeter. The race differed greatly from the varsity race, since it was won by six lengths, with Harvard leading easily all through and with no doubt of the outcome. It was concluded that, in well-trained persons, emotional stress, either alone or in combination with muscular activity, may lead to a highly effective adrenal stimulation and may represent a necessary link in the mechanism of adaptation. Practical application of eosinophil counts made under conditions of standardized stress may well facilitate the identification of persons with unsatisfactory adrenal response to stress. The simplicity of the procedure would permit its use as a screening device. In men with active allergy and in two persons whose spleens had previously been removed no deviation from normal response was detected.

Public Health Reports, Washington, D. C.

66:757-788 (June 15) 1951

Oral Cancer Teaching Program in Dental Schools. R. F. Kaiser.—p. 757.
Cancer Research Facilities Construction Grants Awarded Through National Cancer Institute by Public Health Service. R. G. Meader and W. W. Payne.—p. 762.
Achievement Examination in Subject of Cancer for Medical School Students. H. R. Bierman and J. N. McClelland.—p. 769.

66:789-822 (June 22) 1951

Mouse-Protective Potency Assay of Typhoid Vaccine—As Performed at the Army Medical Service Graduate School. H. C. Batson, M. Brown and M. Oberstein.—p. 789.
*Rapid Flocculation Test for Diagnosis of Trichinosis. J. Bozicevich, J. E. Tobie, E. H. Thomas and others.—p. 806.

Flocculation Test in Diagnosis of Trichinosis.—Bozicevich and co-workers mention shortcomings of earlier complement fixation and flocculation tests in the diagnosis of trichinosis and describe a new flocculation test, which, they hope, will overcome many difficulties. There are descriptions of the preparation of the trichina extract, the stock bentonite, the stock antigen, and the slides and antigen pipets as well as of the test itself. The complement fixation test was used as the standard for the evaluation of the flocculation test. The data so far available do not indicate a superiority of the flocculation test over the complement fixation test, but if they are equally sensitive and specific, the outstanding advantages of the former should make it the test of choice. With the flocculation test, results can be obtained in minutes, and its performance does not require highly trained personnel. It seems likely that the antigen can be prepared commercially, and, if so, it will be possible for almost any laboratory to perform the test.

Virginia Medical Monthly, Richmond

78:281-334 (June) 1951

Toxic Reactions Occurring with ACTH and Cortisone Therapy. C. L. Neale and M. D. Friedenberg.—p. 283.
Survey of Obstetrics by General Practitioners in Small General Hospital. F. D. Daniel.—p. 289.
Hypersplenism in Infancy and Early Childhood: Report of Three Cases. J. E. Mitchell and K. F. Menk.—p. 293.
Hemolytic Anemia Following Caesarean Section Treated by Splenectomy. M. D. Delaney and W. M. Delaney.—p. 299.
Treatment of Epilepsy—Study of 11 Consecutive Cases. J. T. Ransone —p. 303.

Western J. Surg., Obst. & Gynecology, Portland, Ore.

59:141-188 (April) 1951

Synovial Sarcoma: Clinical Impression Obtained from Study of 13 Cases. K. J. Anderson.—p. 141.
Relaxation of Symphysis Pubis in Pregnant Women by Prostigmine. F. E. Emery, W. C. Young, M. R. McCaskill and E. Dodge.—p. 150.
Calculi of Salivary Glands. R. E. McKechnie.—p. 153.
Observations on 20 Years of Experience in Surgery of Sympathetic Nervous System. P. G. Flothow.—p. 156.
Malignancy of Thyroid. M. A. Howard.—p. 163.
Decidual Reactions of Cervix. H. E. Bowles and I. L. Tilden.—p. 168.
Total Gastrectomy in Treatment of Gastric Cancer: Review of 16 Cases. H. M. Biegen.—p. 171.
Care of Eyes in Newborn: Report on 4,500 Cases. M. Leff.—p. 176.

FOREIGN

British Journal of Ophthalmology, London

35:253-316 (May) 1951

*Experiences with Malignant Exophthalmos: Relationship of Condition to Thyrotoxicosis and to Pituitary Thyrotropic Hormone. M. A. Falconer and W. S. Alexander.—p. 253.
Intracapsular Extraction by Kirby's Technique: Results in 60 Cases. J. R. Hudson.—p. 284.
Anatomical Study of Schlemm's Canal and Aqueous Veins by Means of Neoprene Casts: Part I. Aqueous Veins. N. Ashton.—p. 291.
Early Signs of Trachoma Observed by Slit Lamp. Y. Ito and Chiang-Hua Yu.—p. 304.
Modification of Graves' Operation for Epiphora Due to Stenosis of Lacrimal Punctum. J. B. T. Thomas.—p. 306.
Non-Perforating Cyclodiathermy with Cyclodialysis Circumscripta in Glaucoma. V. Čavka.—p. 307.

Malignant Exophthalmos: Relation to Thyrotoxicosis and Pituitary Hormone.—The series of 12 cases of malignant exophthalmos presented here illustrate the wide variations that may occur in the course of this condition and in its response to orbital decompression, thyroid therapy, and other treatments. The authors question whether malignant exophthalmos is a single entity and discuss its therapy and its relation to pituitary thyrotropic hormone and thyroxin metabolism. They feel that malignant exophthalmos is a self-limiting condition, and, although it is connected with the secretion of pituitary thyrotropin and of thyroxin, the relation is indirect and still unknown. Thyroid administration is probably ineffective. The effect of any therapy must not be confused with the spontaneous improvement that occurs in the later stages of the condition. In one type of case the ophthalmic signs become aggravated after thyroidectomy. Therefore, in patients with toxic goiter presenting ocular protrusion as opposed to mere lid retraction, it is wise to avoid thyroidectomy. If the thyrotoxicosis is severe, it is probably safer to treat it by bed rest or by one of the slow nonsurgical methods. In cases of mild or moderate exophthalmos, where the eyeball is not in danger from exposure, radical treatment should be withheld in the hope that a spontaneous remission may occur. Surgical treatment is indicated if exophthalmos becomes pronounced. Lateral tarsorrhaphy may be useful, but in the severest cases, as when chemosis of the conjunctiva and corneal ulceration are present, orbital decompression should be considered.

British Medical Journal, London

1:1217-1278 (June 2) 1951

*Treatment of Arterial Hypertension by Penta- and Hexamethonium Salts: Based on 150 Tests on Hypertensives of Varied Aetiology and 53 Patients Treated for Periods of Two to 14 Months. F. H. Smirk and K. S. Alstad.—p. 1217.
Blood-Group Factors and Physiological Icterus. I. B. Wexler and A. S. Wiener.—p. 1228.
*Angiocardiography in Congenital Heart Disease: Anaesthesia and Technique. D. M. Carnegie.—p. 1230.
Continuing Nursing Care for Small Infant Discharged from Hospital. W. S. Craig, G. A. Kitching, I. G. Davies and C. F. Brockington.—p. 1234.
Carcinoma of Prostate: Comparison of Methods of Diagnosis. J. E. Semple.—p. 1236.
Diagnostic Value of Glucose Content of Serous Pleural Effusions. W. L. Calnan, B. J. O. Winfield, M. F. Crowley and A. Bloom.—p. 1239.
Acute Porphyria with Unusual Features. E. Grossfeld.—p. 1240.

Methonium Salts in Hypertension.—Although the curarizing effects of the methonium series first attracted attention, it was soon found that the pentamethonium and hexamethonium halides, shown to be ganglion-blocking agents, produced reductions in blood pressure in normal and in hypertensive persons. Smirk and Alstad investigated the response to these methonium halides in 150 cases of hypertension of varied etiology. Fifty-three patients have been under treatment for periods of two to 14 months. It was found that there is a close similarity in the hypotensive effects of pentamethonium and hexamethonium bromides, though tests show that hexamethonium bromide is usually slightly stronger in action. These investigators could interchange these substances at approximately the same level of subcutaneous dosage. Drops in blood pressure following methonium injections are influenced by posture, being greater as the patient approaches the vertical. Under comparable conditions patients with higher pressures tend to have greater lowering of blood pressure after hexamethonium bromide injections. Apart from some of the patients with impaired renal function, almost all hypertensives can be controlled by these drugs. Among those with impaired renal function the four selected for treatment were readily brought under control without deterioration in their renal excretory capacity. Repeated administration gives rise to considerable tolerance, so that 5 or 10 times the original dose may be required to produce the same effect. Development of tolerance to hexamethonium bromide gives an equivalent degree of tolerance to pentamethonium bromide, and vice versa. The hypotensive actions of pentamethonium and hexamethonium salts are enhanced with a salt-poor diet (0.2 gm. of sodium in 24 hr.) to such a degree that dangerous reactions may occur if the effects of this potentiation are not allowed for in determining dosage. Hypertensive headaches can be relieved in most patients. There was great improvement of dyspnea, and papilledema and retinal exudates subsided. Pulmonary congestion disappeared, and there are indications of reduction in heart size and electrocardiographic improvement.

Angiocardiography in Congenital Heart Disease.—Some investigators assert that angiocardiography is simple and harmless, but the results in 172 cases at Guy's Hospital contradict this statement. In 115 of these cases, angiocardiography was performed with the patient under general anesthesia and in the remaining 57 with local analgesia and adequate premedication. The ages of these patients ranged from 3 to 37 years. Most patients under 12 required general anesthesia. Three patients died during the procedure—two while under general anesthesia and one who received local analgesia only. A fourth patient died on return to the ward. In another patient, aged 3, signs of cerebral anoxia developed, but finally the child recovered. A history of cyanotic attacks or of attacks of unconsciousness is of grave prognostic significance. All four children who died had had such attacks, as did the child of 3 who had cerebral anoxia. Since even the slightest degree of anoxia involves grave dangers, every effort should be made to prevent oxygen lack. Atropine should be given (1/100 grain [0.60 mg.]) half an hour preoperatively to any patient over the age of 1 year, so that there are no secretions from the tracheobronchial tree. Angiocardiography should be done in an x-ray theater with full surgical and anesthetic equipment to deal with any emergency. The patients should be kept in the x-ray department for at least 15 min. after the operation. Collapse occurred within this period in all four of the fatal cases. For the premedication of older patients pentobarbital and atropine are recommended, and for the younger ones rectally administered thiopental and atropine. Quinidine and a test dose of iodopyracet solution ("diodone") should also be given preoperatively. Cyclopropane, ether, and oxygen, given through a cuffed endotracheal tube, form the anesthetic of choice. Procaine should be administered intravenously through a large cannula inserted into the vein under direct vision both before and after the injection of diodone. Blood pressures and electrocardiographic tracings ought to be recorded.

Canadian Journal of Public Health, Toronto

42:117-168 (April) 1951. **Partial Index**

Antihistamines in Treatment of Common Cold, In Industry. D. C. Bews.—p. 117.
Mortality in Terms of Lost Years of Life. J. H. Doughty.—p. 134.
*Nutrition for Older People. E. W. McHenry.—p. 142.
Oculoglandular Tularemia Transmitted from Contaminated Sewer Water. W. R. N. Lindsay and J. W. Scott.—p. 146.

Nutrition for Older Persons.—The health of older persons is becoming of increasing concern as the percentage of these persons increases in the population. Protein is one type of food constituent that older persons frequently neglect, and meat, cheese, and milk are unlikely to be eaten in adequate amounts. This neglect is due to a mistaken notion that meat is harmful for older persons. Little or no cheese is eaten, because of the old wives' tale that cheese is indigestible and constipating. Little milk is taken, because these persons grew up in an age when the value of milk was not appreciated. Most persons know that protein is needed for growth, but it is generally not realized that there is a constant destruction and loss of body protein that must be replaced from the food supply at any age. The needs of older

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persons for calcium and iron should have particular attention. If calcium intake is insufficient to maintain a fairly constant amount of calcium in the blood, calcium can be withdrawn from the bones, with consequent weakening of the bone structure. It is likely that the increased fragility of the bones of many older persons is the result of a long-standing inadequate supply of calcium in the diet. Most vitamins are needed as much in age as in youth. The author gives a list of food essentials for older persons and stresses that long-standing food prejudices and long-standing faulty food habits form one of the main causes of a poor state of nutrition in older persons.

Deutsche medizinische Wochenschrift, Stuttgart

76:725-756 (June 1) 1951. **Partial Index**

Experiences with Trichlorethylene as Anesthetic in Childbirth. H. Hosemann and T. Hickl.—p. 725.
Function of Suprarenals and Tuberculosis. K. H. Pfeffer, E. Scherer and H. Staudinger.—p. 727.
Ophthalmologic Complications in Canicola Fever (Leptospirosis). H. Beleke and R. Bandau.—p. 729.
*Vascular Component in Clinical Picture of Epilepsy. E. Förster.—p. 732.
*Endoscopic Transpleural Sympathectomy According to Kux in Treatment of Duodenal Ulcer. C. Job and R. Villinger.—p. 734.
*Therapeutic Use of Procaine Hydrochloride: Clinical Experiences. R. Mancke, W. Masuch and G. Orzechowski.—p. 737.

Vascular Component of Epilepsy.—Förster demonstrates that in regard to symptoms there is a parallelism between epilepsy and brain lesions with a vascular component, such as in strangulation, carbon monoxide poisoning, and disorders of the vessels of the brain. Impairment of the blood perfusion of the brain is an essential factor in all these conditions. The parallelism in the motor symptoms during the recovery phase of strangulation, carbon monoxide poisoning, and convulsive attacks, to which may be added temporary pyramidal symptoms, suggests that vascular factors are chiefly responsible. Penfield has pointed out that vasoconstriction may persist in the brain for a time after the epileptic attack has subsided.

Endoscopic Transpleural Sympathectomy for Duodenal Ulcer.—The endoscopic transpleural sympathectomy that Kux recommended for the treatment of duodenal ulcer in 1948 has been used at the clinic of the University of Imsbruck for three years. Kux himself has performed it in about 350 cases without a fatality. A thoracoscope is introduced into the pleural cavity through an intercostal space. The opening made into the thoracic wall is hardly more than 1 cm. long. A preliminary pneumothorax collapses the lung, so that the portion of the sympathetic that passes through the costovertebral sinus becomes visible. After the sympathetic and splanchnic have been divided with the cauter, the pneumothorax is suctioned off. The method requires only about 15 min., can be carried out with the patient under local anesthetic, and causes no disfiguring scars. Furthermore, it involves almost no risk for the patient; most of the patients can be discharged from the hospital three days after the intervention and can resume their occupations in a short time. This treatment is restricted to duodenal ulcers, because with gastric ulcers the possibility of malignancy must always be kept in mind, particularly if the patient is over 40. In a follow-up of 110 of the patients in whom Kux had performed a transpleural sympathectomy, results were found to be the same, regardless of whether the operation had been done only on the right side or on both sides, provided it had been radical. A few patients who had had the operation on the right side, later required sympathectomy also on the left side, because of recurrence of symptoms, but the expected improvement was still not realized. In all of these patients the peptic ulcer had begun before the age of 20. Nearly all the other patients who had undergone radical resection on the left side, when a nonradical operation on the right side had been followed by recurrence, remained free from symptoms after the second intervention. Radical sympathectomy on the right side is necessary for the success of the intervention, but bilateral radical operation is unnecessary. Radical operation on the left side should be done only if for technical reasons the operation could not be radical on the right side. Patients in whom the ulcer developed before the age of 20 have a much less favorable prognosis than those in whom the ulcer develops later in life.

Procaine Hydrochloride Treatment.—The authors compared the therapeutic effect of a combination of procaine hydrochloride and solution of honey with that of procaine hydrochloride alone in allergic disorders (bronchial asthma, colic, and diarrhea). Five patients were studied. It was found that the preparation containing the honey was tolerated better than the plain solution of procaine hydrochloride. The latter must be given very slowly, if the injection is made intravenously, whereas the honey compound can be injected more rapidly. Apparently the honey compound is not quite so effective as procaine hydrochloride alone, but the difference is apparently only quantitative and can be compensated for by larger doses. The honey and procaine hydrochloride proved effective in all types of spastic conditions. Its undesirable secondary effects were generally mild.

Irish Journal of Medical Science, Dublin

305:193-240 (May) 1951

Surgery of Mitral Stenosis. P. T. O'Farrell and others.—p. 193.
Calcification of Left Auricle. P. T. O'Farrell.—p. 211.
Hearing-Aid Clinics and Rehabilitation of the Deaf. R. S. Stevenson.—p. 213.
*Oesophagectomy. (With Report on Successful Case in Which Presternal Gastro-Oesophageal Anastomosis was Performed.) F. J. Morrin.—p. 225.
Visceral Thrombophlebitis Migrans: Report of Case and Review of Literature. P. Corridan and R. Mulcahy.—p. 232.

Esophagectomy.—After briefly reviewing the symptoms of carcinoma of the esophagus, Morrin discusses the technical difficulties encountered in the surgical treatment. He evaluates different surgical techniques and says that he prefers the operation suggested by Taylor, because it is applicable to a majority of cases, it can be done in stages, it has fewer difficulties of approach, and it obviates the fatal risk from leakage of an intrathoracic anastomosis. He describes a case in which he performed this three-stage operation with satisfactory results. In the first stage he resected the thoracic esophagus and created a cervical esophagostomy and epigastric cardioesophageal stoma. In the second stage the stomach was mobilized, brought out through the abdominal wall, and passed upward through a subcutaneous tunnel in front of the sternum to meet the esophagostomy. In the third stage the cervical esophageal stump was anastomosed to the stomach and continuity of the alimentary tract was reestablished. Three months later the patient was eating without difficulty and living a normal life.

Journal of Laryngology and Otology, London

65:317-396 (May) 1951

Influence of Heredity on Pneumatization of Temporal Bone. H. W. Schwartz.—p. 317.
Nerve Supply of Laryngeal Muscles. A. F. Williams.—p. 343.
Trotter's Syndrome and Associated Lesions. N. Asherson.—p. 349.
*Tuberculosis of Middle Ear: Treatment with Streptomycin. A. R. Dingley.—p. 367.

Streptomycin in Tuberculosis of Middle Ear.—The first case reported in this paper was that of a boy, 6, who while in bed for 10 months for a tuberculous pulmonary lesion had a rupture of the right tympanum followed by four weeks of profuse discharge. Streptomycin therapy (1 gm. daily in divided doses) was started 10 days after his admission to the hospital and was continued for three months. The aural discharge lessened after two or three weeks of treatment, and it was found that the tympanic membrane was bulging and had a perforation that was choked with a granular mass. There were three miliary tubercles in the tympanic membrane. Through the intact anteroinferior segment yellowish areas of tuberculous material were seen. After the granular mass was extruded through the perforation, there was an increased discharge, which then ceased, followed by healing of the drum. The membrane was normal, except for a thin scar, and hearing was unimpaired. The pulmonary lesion also seems to have cleared. The second case was that of a girl of 21 who had been under treatment for pulmonary tuberculosis for two years. A rupture of the right tympanum followed two weeks after an operation to compress the lung. After six weeks of otorrhea, the ear was painful, with profuse mucopurulent discharge. A greyish membrane could be seen through a large perforation. Much destruction of membrane and ossicles had occurred. Tubercle bacilli were recovered from the aural dis-

charge. The patient was given 1 gm. of streptomycin daily and 12½ grains (0.78 gm.) of paraaminosalicylic acid. A total of 40 gm. of streptomycin was administered in six weeks, at the end of which time the ear was dry and healthy, but with much destruction of membrane and ossicles remaining. The hearing, though much diminished, was better than had been expected. Streptomycin apparently played a vital part in the improvement of these two patients. Early diagnosis and prompt treatment is the most important factor in preservation of hearing and prevention of destruction of tympanic structures.

Klinische Wochenschrift, Heidelberg

29:333-364 (May 15) 1951. **Partial Index**

*Anemia Refractory to Iron, but Responsive to Cobalt Therapy: Question of Occurrence of Thalassemia Minor in Germany. L. Heilmeyer, W. Müller and H. Schubothe.—p. 333.
Morphology, Physiology and Pathology of Thrombocytes. H. Braunsteiner.—p. 335.
*Pathogenesis of Endocrine Syndromes in Tuberculous Meningitis. P. Bünger.—p. 338.
*Epidemiology of Toxoplasmosis: Dogs as Source of Infection of Human Toxoplasmosis. E. Otten, A. Westphal and E. Kajahn.—p. 343.
Pathogenesis of Hypochromic Anemia Following Gastric Resection. D. Remy.—p. 346.

Thalassanemia in Germany.—Heilmeyer and associates present the histories of three patients with characteristic symptoms of the mild form of thalassanemia (familial erythroblastotic anemia), also known as Mediterranean, or Cooley's anemia. This anemia is of the hypochromic type. The blood smear shows many target cells in the presence of anisocytosis and poikilocytosis, reduced diameter, and reduced volume of erythrocytes. The osmotic resistance of erythrocytes in hypotonic solution of sodium chloride is greatly reduced. The anemia is resistant to iron therapy but improves noticeably with cobalt therapy. Icterus and splenic tumor were absent in the patients described. This is understandable in view of the fact that the anemia was mild. There were no persons of Mediterranean blood in the ancestry of these patients. Thus it must be assumed that this form of anemia may occur in Germans. Similar blood pictures were observed in the parents and siblings of two of the patients.

Endocrine Disturbances in Tuberculous Meningitis.—The examination of 120 patients with tuberculous meningitis who had been treated with streptomycin, paraaminosalicylic acid, and amithiozone revealed endocrine symptoms, which in view of their multiformity indicated disturbances in controlling centers. Four cases are reported in detail. One is of a man, 42, with obesity of the general dystrophic type, impotence, and hemianopsia on the left, as well as disturbances in carbohydrate metabolism. The second patient, a boy, 16, had dystrophia adiposogenitalis with bluish red striae and impairment of the oculomotor function. The third patient, a woman, 26, had marasmus due to diencephalic disturbances with cachexia, hypertrichosis, and left-sided hemianopsia. The fourth patient, a man, 49, had diabetes insipidus and disturbances in carbohydrate metabolism. A review of the literature shows that similar cases occurred earlier, so that streptomycin and the chemotherapeutic substances cannot be held responsible for the development of these symptoms. Vascular processes, which nearly always occur in the forms of meningitis and which take a prolonged course, are probably the pathogenic factors in these endocrine disturbances, and they probably cause ischemia and malacia in the region of the sympathetic nuclei of the diencephalon. Thus the endocrine symptoms are a manifestation of a disturbance in the diencephalic system.

Dogs as Source of Human Infection with Toxoplasmosis.—A number of reports in the literature suggest dogs as the possible source of infection in human toxoplasmosis. Otten and associates examined 122 dogs for the presence of toxoplasmosis by means of the Sabin-Feldman serum dye test. The test was positive in 49 dogs. This high incidence of positivity is explained by the fact that many of the dogs tested had symptoms suggestive of toxoplasmosis, such as neuritis, partial paralysis, tonoclonic convulsions, and gastroenteritis with diarrhea. Some latent infections were found. It has been estimated that from 2% to 5% of the dogs in Hamburg are infected with toxoplasmosis. The Sabin-Feldman dye test was also made on 38 persons who had been in contact with 23 dogs in which this test had been positive. Twenty-three of the 38 persons gave a positive reaction to the test. Five dog-owners who were tested within eight days of the appearance of clinical manifestations of toxoplasmosis in their dogs gave negative reactions. The dogs in question showed the neurological picture of toxoplasmosis. Two of six dog-owners, whose dogs had the chronic form of toxoplasmosis with predominantly neurological signs, reacted positively to the test. Six of eight persons who had been in contact with four dogs with acute toxoplasmosis accompanied by severe diarrhea had positive reactions. Ten of 11 persons who had been in contact with dogs having a mixed symptomatology indicating neurological and general systemic infection with toxoplasmosis gave a positive reaction. Thus it appears that those dogs in which toxoplasmosis produces ulcerative proctitis and diarrhea play an especially important role in the transmission of the disease to humans.

Krebsarzt, Vienna

6:129-184 (June 1) 1951. **Partial Index**

"Collision Tumors" of Stomach. S. Battaglia.—p. 129.
Importance of Examination of Vaginal Secretion for Detection of Cancer of Female Genitalia. R. Bayer.—p. 147.
*Incidence and Type of Primary Cancer of Liver. J. Zeithofer.—p. 154.
Irradiation Therapy in Cancer of Larynx in Light of International Research. E. Ruckensteiner.—p. 161.

Incidence and Form of Primary Cancer of Liver.—The incidence and form of primary cancers of the liver were studied in the necropsy material of the Pathologic Institute of the University of Vienna. It was found that cancer of the liver is more frequent in men than in women and that it is particularly frequent in the age group from 50 to 70. Nodular forms accounted for 67% of the cancers and diffuse forms for 33%. Histological studies revealed that 76% of the carcinomas were of the hepatocellular and 24% of the cholangiocellular type. An apparent increase in the incidence in cancer of the liver, which involved only the diffuse forms, cannot be explained completely by the increased incidence of hepatic cirrhosis and its malignant degeneration nor by the increase in persons in the higher age groups. It is suggested that the presence of cancerigenic dyestuffs in foods, such as butter yellow, may play a part. These substances might favor the development of carcinoma in cirrhotic liver, for instance, where regenerative processes are already increased.

Lancet, London

1:1133-1186 (May 26) 1951

Physical Exercise: Its Clinical Associations. A. Abrahams.—p. 1133.
*Sequelae of Radical Gastric Resections: Clinical and Metabolic Findings in 35 Cases. R. H. F. Brain and F. A. R. Stammers.—p. 1137.
Prevention and Treatment of Travel Sickness with Promethazine Chlorotheophyllinate. J. Harper.—p. 1141.
Fluid Mechanics and Dynamics of Transfusion: Rapid Replacement of Severe Blood-Loss. D. G. Melrose and R. Shackman.—p. 1144.
Sickle-Cell Anaemia in Greece. C. Choremis, N. Zervos, V. Constantinides and L. Zannos.—p. 1147.
Stenosing Tendovaginitis at Radial Styloid Process: Review of 30 Cases. D. A. C. Reid.—p. 1149.
"Tennis Thumb": Tendinitis with Calcification in Flexor Pollicis Longus. M. C. Oldfield.—p. 1151.
Curettage in Diagnosis of Cervical Cancer: Modified Spoon Curette. A. F. Anderson.—p. 1152.
Osteomyelitis Due to Friedländer's Bacillus. D. A. Muskat and M. Findlay.—p. 1154.
Lethal Effect of Morphine in Chronic Cor Pulmonale. N. J. Roussak.—p. 1156.
Streptomyces Fermentation Derivatives in Acute Leukaemia. R. D. Barnard.—p. 1157.
Fibrosarcoma of Tongue After Interstitial Irradiation: Report of Case. P. Deller.—p. 1159.

Sequelae of Radical Gastric Resections.—Advances in surgical technique have made possible increasingly radical resections, but the question must be raised whether such extensive eradications are psychologically and physiologically justified. The authors investigated in 35 patients the sequelae of total or near total gastrectomies, particularly the failure of the patient in these cases to gain weight and strength and their liability to diarrhea, anemia, and deficiencies of vitamin-B complex. They list the possible causes of the disturbances observed, chiefly the difficulties of ingestion and defective absorption. Follow-up observations on 33 patients are summarized. Studies on the fat metabolism suggest that the main causes of wasting after radical

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gastrectomy are poor capacity for food, associated with the dumping syndrome, and malabsorption of fat. To compensate for these defects, a diet with a high fat content is recommended. From 100 to 120 gm. of fat should be eaten daily, with a correspondingly high caloric intake and multiple small meals, so that fat is taken eight to 10 times in the 24 hours. The patient should not drink with meals and should avoid sugar, protein hydrolysates, and other substances capable of producing a high intrajejunal osmotic pressure, and withdrawing fluid from the bowel, thus causing further distension and perhaps inducing the dumping syndrome. With this regimen, some patients in the present series have managed to eat more than their normal preoperative intake and have therefore gained weight. The blood picture after radical gastrectomy is characterized by a high incidence of macrocytosis. No evidence of iron deficiency was found. Vitamin-B deficiencies can be prevented by the routine administration of vitamin-B complex and by the eradication of septic processes such as the multiplication of organisms in the upper alimentary tract and infections in the subphrenic space or pleural cavity. Large doses of nicotinic acid and riboflavin, given before and after operation, have reduced the incidence of vitamin-B deficiency.

1:1187-1238 (June 2) 1951

Physical Exercise: Its Clinical Associations. A. Abrahams.—p. 1187.
Radical Cure of Inguinal Hernia in the Elderly. H. Dodd.—p. 1192.
Orthostatic Albuminuria: Time-Saving Method of Diagnosis. A. Watson.—p. 1196.
Total Colectomy in One Stage for Ulcerative Colitis. B. N. Brooke.—p. 1197.
*Treatment of Tuberculous Cervical Adenitis with Para-Aminosalicylic Acid. G. J. Morris and R. G. Prosser-Evans.—p. 1199.
*Toxoplasmosis in Hares in Denmark: Serological Identity of Human and Hare Strains of Toxoplasma. M. Christiansen and J. C. Siim.—p. 1201.
Bowel Rhythm in the Healthy Infant: Its Suggested Relationship with Chronic Constipation. I. Gordon.—p. 1203.
Ophthalmoscopic Detection of Microfilaria of Onchocerca Volvulus. J. W. R. Sarkies.—p. 1205.
Lipoid Pneumonia (Non-Inhalation) in Carcinoma of Lung Treated by Radiotherapy. S. J. De Navasquez, J. R. Trounce and A. B. Wayte.—p. 1206.
Neuromuscular Incoordination of Swallowing in the Newborn. J. C. Macaulay.—p. 1208.
Changes in Cerebrospinal Fluid After Pneumo-Encephalography. E. R. Bickerstaff.—p. 1209.
Suppurative Hepatitis and Diaphragmatic Paralysis. J. W. Todd.—p. 1210.

Paraaminosalicylic Acid for Tuberculous Cervical Adenitis.—Fifty-one patients with tuberculous cervical adenitis were treated by aspiration of pus and instillation of sodium paraaminosalicylate in the past two years. A 10 year survey of results of other methods provided a basis for comparison. The abscess was aspirated with a large-bore needle inserted directly into its superficial wall. The contents were completely evacuated, and up to 1 ml. of a 20% solution of sodium paraaminosalicylate was instilled into the abscess cavity through the aspirating needle. On withdrawal of the needle very little of the solution escaped, even when under moderate tension. Aspiration and instillation were repeated at weekly intervals, until the contents of the abscess cavity became serous and no further pus formed. In those cases in which a sinus had formed along the needle track, up to 1 ml. of a fairly thick sterile jelly containing 20% sodium paraaminosalicylate was injected through the orifice of the sinus. If a sinus ulcer developed, a cream of similar strength was applied superficially and renewed daily, until the granulation tissue of the ulcer floor was clean. Sodium paraaminosalicylate apparently reduced significantly the area and depth of residual scarring in suppurative tuberculous cervical adenitis. More than half the treated patients were cured, with little or no evidence of the original lesion remaining in the skin. The healing time was substantially reduced. The results, in general, compare favorably with those achieved by more active measures (curettage), and the patient need not be hospitalized.

Toxoplasmosis in Hares in Denmark.—Since 1935 diseases in wild animals have been systematically investigated in Denmark. This made it possible to examine many wild hares found dead in the open field or shot in a sick condition. Some of these hares were found to have toxoplasmosis. Histological examination showed Toxoplasma in large numbers in the organs with pathological changes (especially the spleen) and also in the brain. Toxoplasma strains were isolated by inoculating intraperitoneally into mice 1 ml. of a 10% suspension of spleen from infected animals, within 24 hr. after they had died. Toxoplasmosis in hares in Denmark has its maximum incidence in the period January to March. It occurs in hares as an acute fatal systemic disease; only a few weak positive serological reactions have so far been found in healthy hares. The Toxoplasma of hares appears to be serologically identical with the human strain RH, and is equally pathogenic. Consequently, in handling recently dead toxoplasmic hares there is a risk of infection. Pregnant women should not handle recently shot hares. Animals frozen at —30 C. and later thawed do not seem to be infective.

Lyon Chirurgical

46:385-512 (May-June) 1951. **Partial Index**

*Results of Conservation of the Sphincter in Surgical Intervention for Cancer of the Rectum. P. Santy, P. Michaud and P. Replumaz.—p. 385.
Phlebography of Pelvis by Injecting the Contrast Medium Through the Pubis. J. Ducuing, P. Guilhem, D. Enjalbert and others.—p. 393.
Experimental Study on Partial or Total Ligature of the Aorta at Various Levels. R. Leriche, J. Kunlin and C. Boely.—p. 405.

Surgical Treatment of Cancer of Rectum.—Conservative operations were done in 136 patients with cancer of the rectum, consisting of resection in 31 and total excision with meticulous dissection of the mucosa of the anal canal and transsphincteral lowering of the sigmoid flexure in 105. The most important advantage of the transanal total excision is that colostomy is completely eliminated. The abdominosacral approach was used in 115 cases and the sacral approach in 21. There were only 12 operative deaths, an operative mortality rate of 8.8%. Of 71 patients with cancer of the rectum subjected to nonconservative operations, 10 died, an operative mortality rate of 14%. Late results in patients subjected to conservative operations by lower approach were highly satisfactory, since of 19 patients subjected either to resection or to transanal excision, 12 (63%) survived for more than five years, while of 52 patients operated on by abdominosacral route only 20 (40%) survived for more than five years. A questionnaire was sent to all the surviving patients in an attempt to ascertain the functional results of the conservative surgical treatment. Of 70 patients from whom answers were received, 46 had excellent function of the sphincter muscles with complete continence and perfect anatomic condition of the anus, 17 had impaired function, and some required dilatation for stenosis. Seven patients had complete incontinence, caused either by sacral fistula with anal stenosis, or complete sloughing of the lowered segment, which required the establishment of a left iliac anus. Generally speaking, the authors believe that the preservation of the anal function in the exeresis of carcinoma of the rectum is justified.

Medical Journal of Australia, Sydney

1:497-532 (April 7) 1951

Lewis Blood Antigens and Antibodies. R. T. Simmons and R. Jakobowicz.—p. 497.
Carcinoma of Ampulla of Vater. C. Osborn.—p. 501.
Limitations of Pure Psychogenesis. B. Mulvany.—p. 505.
Nitrous Oxide-Thiopentone-Curare Anaesthesia: Preliminary Report on Apparently Satisfactory Technique. R. V. Pratt.—p. 510.

1:533-568 (April 14) 1951. **Partial Index**

Management of Flail Lower Limb Following Poliomyelitis. E. Price.—p. 540.
Some Observations on 100 Cases of Ankylosing Spondylitis. L. J. A. Parr, P. White and E. Shipton.—p. 544.

Nederlandsch Tijdschrift v. Geneeskunde, Amsterdam

95:1341-1404 (May 5) 1951. **Partial Index**

Use of Preserved Calf Bone for Transplantation into Human Subjects. W. G. Meiss.—p. 1349.
*Effect of Cola Drinks Containing Caffeine. D. A. A. Mossel.—p. 1357.
*Transplantation of Ureters into Large Intestine. J. F. Ort and R. Sajidiman.—p. 1366.

Action of Cola Drinks with Caffeine Content.—Some cola drinks prepared in the Netherlands contain caffeine in amounts varying from 20 to 75 mg. per 200 cc. bottle, whereas some other nonalcoholic drinks have no caffeine. It should be made obliga-

tory to declare the contents of nonalcoholic drinks on labels. As long as it has not been demonstrated that the caffeine that is added to cola drinks is not harmful when these drinks are taken over long periods, children, persons with gastric disorders, and all those for whom caffeine is likely to prove harmful should be advised not to take these drinks. The fact that some cola drinks contain phosphoric acid at the very low pH of 2.5 involves the added risk that their consumption may cause dental erosion.

Transplantation of Ureters into Large Intestine.—A new technique for the implantation of the ureters into the intestine is recommended. The method involves: 1. Extraperitonealization of the surgical field. 2. Implantation of the extraplevic portion of the ureters, because it is difficult to displace the distal portion with its more or less individual vascularization. In this way, the implanted portion of the ureter retains an adequate blood supply and the dangers involved in inadequate circulation are avoided. 3. Implantation of both ureters into a receptacle formed from the sigmoid, which is more or less separate from the other portions of the intestinal tract. The adequacy of this method is proved by the fact that patients in whom it has been employed are alive and well five years after treatment.

95:1533-1600 (May 26) 1951. Partial Index

Body Surface Temperature. J. W. H. Mali.—p. 1544.
Multiple Primary Malignant Tumors. G. H. W. Jordans.—p. 1555.
Echinococcosis of Spleen. A. Pasma.—p. 1560.
*(Pseudo?) Liver Abscess and Tumor of Colon Caused by Lamblia Intestinalis. W. Beukema.—p. 1568.

Giardiasis as Cause of Liver Abscess and Tumor of Colon.—Giardiasis (lambliasis) was discovered in a man, 47, in whom an abscess of the liver developed that perforated through the diaphragm. Exudate developed in the pleural cavity, and there was infiltration into the middle lobe of the right lung. Two series of treatments with quinacrine hydrochloride resulted in complete clinical recovery. The complaints described arose a few months after resection of the colon because of a tumor, which on pathological-anatomic examination appeared to consist of nonspecific inflammatory tissue. It is possible that this tumor also had been caused by Giardia. The author feels that in cases in which no explanation can be found for serious abdominal complaints, fresh feces and warm duodenal contents should be searched for Giardia Lamblia.

Nordisk Medicin, Stockholm

45:705-744 (May 9) 1951. Partial Index

*Scleroderma. V. Dreyer.—p. 705.
*Frontal Lobotomy: Psychiatric Experiences. I. Blomqvist and O. Börjeson.—p. 710.
*Frontal Lobotomy: Surgical Experiences in 360 Cases. K. Hilson Holmdahl.—p. 714.
Retrograde Amnesia After Electroshock Treatment. H. Kehlet and V. Lunn.—p. 716.
Fatal Complications After Bulbar Tractotomy. J. Cammermeyer.—p. 719.
Electroencephalographic Studies on Cramp Threshold in Children of Epileptics. B. Harvald.—p. 726.
Treatment of Psychopathic Criminals. G. K. Stürup.—p. 730.
Polyostotic Fibrous Dysplasia (Albright's Syndrome) with Multiple Tumors of Soft Tissue. H. C. Arnesen and L. Nitter.—p. 735.

Scleroderma.—Dreyer deals especially with the internal manifestations of scleroderma. While the disease is relatively infrequent, particularly in the generalized form, its varied symptomatology, obscure etiology and pathogenesis, and its relation to other systemic diseases have received much attention in the literature. It occurs twice as often in women as in men. There are circumscribed and diffuse forms. The visceral manifestations appear in the latter. Scleroderma with internal changes has a marked chronic course. The organs oftenest affected are the esophagus, heart, and lungs. The characteristic changes in scleroderma appear in the blood vessels and in the connective tissue. The small arteries and arterioles especially are affected, with proliferation of intima, and in recent cases, hyperplasia of media, which gradually is followed by fibrosis of media and frequently by thickening of adventitia. In the connective tissue the loose collagenous fibers are transformed into dense homogeneous fibrous tissue; the edema of the tissue seen in the earlier stages is supplanted by a spreading hyperplasia of the collagenous fibrils, with degeneration and atrophy of all other connective tissue elements. Since the etiology and in part also the pathogenesis of scleroderma remain unexplained, treatment rests on an empirical basis. Scleroderma, though most often progressive, may show definite variations in its course. Spontaneous remissions are not unusual, and the disease may remain stationary after a shorter or longer time of development. The view is supported that scleroderma is a systemic disorder localized to the collagenous connective tissue.

Frontal Lobotomy: Psychiatric Experiences.—Bilateral frontal lobotomy was performed in 1946 and 1947 in 131 patients, aged 19 to 71, with predominantly advanced cases with poor prognosis, in which the usual methods of treatment had brought no lasting benefit. There were six deaths. Sixteen patients were discharged as able to work, 15 were discharged to their homes, seven to homes for the aged or the like, 49 were more or less improved but not fit for discharge, and five became worse. Observation for an average of over three years showed that complications as described in the literature developed in a number of cases. Lasting psychic changes in the form of typical frontal lobe syndrome, with indolence, euphoria, and apathy, were seen in a few instances. Frontal lobotomy in selected chronic cases, where other less radical methods of treatment have proved ineffective, is considered a valuable procedure. With interested surgeons good therapeutic results can be achieved with low mortality rates.

Frontal Lobotomy: Surgical Experiences in 360 Cases.—Report is given on 360 lobotomies performed in a general surgical department, with nine deaths, of which five were due to intracranial hemorrhage, two to meningoencephalitis, and two to marasmus. A graduated blunt probe was used, and the incisions in dura were reduced to small punctures. Dura and galea aponeurotica were not sutured. Holmdahl states that in most cases the blood pressure sinks momentarily on incision of the white matter and afterward slowly rises. Absence of the fall in blood pressure may be a sign of incomplete incision of the white substance. Rapid increase in blood pressure after the intervention is an important sign of postoperative intracranial hemorrhage and is an indication for operative revision. More marked hypertension and arteriosclerosis are relative contraindications. Continuous postoperative control of the blood pressure is of the greatest importance. Roentgenologic localization of the ventricular system before the intervention and injection of contrast substance before control of complicating hemorrhage are unnecessary and not without danger.

Obst. y Ginecol. Lat. Americanas, Buenos Aires

9:131-188 (May) 1951. Partial Index

*Carcinosarcoma of Uterus. J. C. Ahumada, R. Sammartino and L. A. Arrighi.—p. 131.

Carcinosarcoma of Uterus.—In the last 20 years Ahumada and collaborators observed 27,000 patients in a gynecologic clinic of Buenos Aires. Carcinosarcoma of the uterus was found in 10 cases (0.04%). The authors define carcinosarcoma of the uterus as a mixed tumor consisting of both carcinoma and sarcoma cells with or without predominance of one type of cell. They divide carcinosarcoma into two groups, namely, collision carcinosarcoma and composition carcinosarcoma. In collision carcinosarcoma there are distinct carcinomatous and sarcomatous zones in the tumor. Where these come in contact there is mutual invasion of neoplastic cells. The two tumors appear to originate at separate sites. The gross types of tumor most frequently found are diffuse carcinoma and polypoid sarcoma. The predominant histologic types seen in tumors of the cervix are squamous cell carcinoma and polypoid or fibroblastic nodular sarcoma. When the tumor develops in the body of the uterus it assumes the form of cylindrical cell carcinoma and undifferentiated sarcoma. Composition carcinosarcoma of the uterus does not have a characteristic macroscopic appearance. Microscopically it shows an intermingling of carcinomatous and sarcomatous cells, either one of which may predominate. The symptoms are similar to those of other tumors of the uterus. The diagnosis is made by microscopic study of tissues taken by

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curettage or of the surgically removed tumor. The metastases are sarcomatous, carcinomatous, or carcinosarcomatous. The treatment is surgical. When the tumor is in the cervix the treatment consists of an operation of the type used in cancer of the endometrium. When the tumor is in the body of the uterus Wertheim's operation, followed in all cases by x-ray treatment, is indicated. In the cases reported by the authors the tumor was of the collision type in three cases and of the combination type in seven. Tumors of the collision type have a better prognosis than those of the combination type, which are very malignant.

Philippine Medical Association Journal, Manila

27:155-202 (March) 1951

Stress. A. B. M. Sison.—p. 155.
Scleroma (Rhinoscleroma): First Case Report in the Philippines. M. G. Tan and S. A. Simuangco.—p. 163.
Venereal Disease in Female Vagrants. A. A. Lozano.—p. 171.
Hypersplenism. G. L. Reyes and A. E. Jose.—p. 175.
Can the Method of Medical Teaching be Improved? R. V. Guiang. —p. 180.

Praxis, Bern

40:455-478 (May 31) 1951. **Partial Index**

*Abortifacient Effect of Ovarian Hormone Preparations. E. Läuppi. —p. 455.
Treatment of Anal and Genital Eczema in General Practice. G. H. Klövekorn.—p. 459.
Clinical Experiences with the Combined Administration of Calcium and Vitamin C. E. Stangl.—p. 460.

Abortifacient Effect of Ovarian Hormone Preparations.—In connection with a law suit involving abortion, the question whether ovarian hormone preparations could induce abortion had to be decided. One of the substances in question was an estradiol preparation prepared for oral administration; the other was a fluid extract of the total ovary, which contained all ovarian hormones but was free from protein. The latter preparation is indicated for use in sexual infantilism, menopausal disturbances, dysmenorrhea, oligomenorrhea, and amenorrhea. Both preparations contain estrin, which increases the blood perfusion of the uterus as well as its responsiveness to the stimulus for contractions. A predominance of estrin over its antagonist, the corpus luteum hormone, supposedly is responsible for the induction of labor pains (uterine contractions). This paper presents three cases in which women had taken both of the aforementioned products in efforts to produce abortion. The oral estradiol preparation produced neither toxic symptoms nor signs of a beginning abortion. However, the intake of the fluid extract of the total ovary was followed by palpitation, tinnitus, vertigo, "blacking out," cold sweat, nausea, and, in one instance, by repeated vomiting. Genital hemorrhages followed in all three cases, and, in the two cases in which pregnancy was certain, these hemorrhages were accompanied by spasms resembling uterine contractions and the discharge of a mass or a fetus. The fact that no other abortifacients had been used in addition to the ovarian hormones and that the patients had been well before the hormones had been taken and that the abortion followed within two or three days after the intake of the fluid ovarian hormone extract is regarded as indicative of an abortifacient effect. To be sure, the fluid extract had been taken in a dosage many times that used in the therapeutic application of this extract.

Presse Médicale, Paris

59:761-780 (June 2) 1951

Diaphoretic Form of Left Ventricular Failure. C. Lian and Brawerman. —p. 761.
*Selective Separation and Transfusion of Morphologic Elements of Blood. J. Julliard, B. Maupin, P. H. Bonnel and others.—p. 762.
Postoperative Care of Patients with Extrapleural Pneumothorax. J. Catta, G. Picard-Leroy and A. Massendari.—p. 763.

Transfusion of Morphologic Elements of Blood.—The authors describe the techniques used to separate the morphologic elements of blood from plasma and the therapeutic results obtained from their intravenous administration. Red blood cells are separated from plasma by centrifugation and used therapeutically after simple dilution or after several washings with isotonic sodium chloride solution to free them of plasma and white blood cells. Leukocytes can be obtained in a concentrated suspension by pipetting off the superficial layer of white cells from the red cells after routine centrifugation. This suspension also contains numerous red cells and platelets. White cells can further be separated from red cells by polyvinyl pyrrolidone (P. V. P.) sedimentation and from both red cells and platelets by controlled centrifugation. The authors gave 80 transfusions of concentrated red cells and 140 transfusions of washed red cells to patients with various anemias and acute leukemias. The red cells were more effective and less expensive than whole blood, introduced a smaller volume of fluid in patients with circulatory difficulties, and were well tolerated. They were especially effective in hemolytic anemias. Twenty-six transfusions of concentrated suspensions of leukocytes obtained by ordinary centrifugation or polyvinyl pyrrolidone sedimentation were administered to 10 patients with various blood dyscrasias. Although the cells were obtained from persons of the same blood type as the patient, chills and fever occurred in several recipients. Treatment had no effect in two cases of acute agranulocytosis nor in three cases of acute leukemia. There was transitory improvement in a severe case of infantile agranulocytosis and in one case of chronic neutropenia. Prolonged improvement occurred in two cases of chronic neutropenia and in one case of aplastic anemia with purpura. Following transfusion an immediate paradoxical leukopenia was frequently observed. The beneficial effect in these cases was presumably due either to the supplying of essential leukocytic material or to specific stimulation of the bone marrow. The crude white cell suspension obtained by ordinary centrifugation was more useful when the patient had a deficiency of all the formed elements, while the purer suspensions were used in simple agranulocytosis.

Proceedings of Royal Society of Medicine, London

44:347-422 (May) 1951. **Partial Index**

Studies in Physiology of Awareness: Oximetric Evidence of Role of Anoxia in Certain Psychiatric States. J. W. L. Doust.—p. 347.
Approach to the Nasopharynx. C. P. Wilson.—p. 353.
Problem of "Clicking Jaw." V. E. Ireland.—p. 363.
*Assessment of Flaxedil (Gallamine Triethiodide, B. P.). A. G. Doughty and W. O. Wylil.—p. 375.

"Flaxedil."—"Flaxedil," or gallamine triethiodide (1,2,3-tri [diethylaminoethoxy] benzene triethyliodide), is a synthetic curarizing agent. It has several clinical advantages over tubocurarine. With flaxedil there is a greater margin between muscular relaxation and diaphragmatic paralysis. Flaxedil has an equally effective but shorter period of action. Its action is more readily and rapidly reversed by neostigmine. It does not lower the blood pressure. This assessment illustrates that flaxedil is a very versatile and safe muscle relaxant. The fact that it is a short-acting curarizing agent with an effective antidote has widened the field of application for this type of drug. Its short period of action is not only one of its main advantages but also its main limitation. Though it can be used for prolonged relaxation and for control of respiration, for frequent injections, the longer-acting tubocurarine seems to be more suitable. Flaxedil's one main disadvantage—tachycardia—has been observed in many patients under thiopental sodium, nitrous oxide, and oxygen anesthesia, but not to the same extent under cyclopropane. Though the rapid pulse may be disquieting to the anesthetist, and may, in theory, mask danger signals of the patient's general condition, these investigators have been unable to attribute to tachycardia any undesirable effects.

Revista Paulista de Medicina, São Paulo

38:91-182 (Feb.) 1951. **Partial Index**

Tetanus Following Induced Abortion. I. Nussenzveig, O. Stersa, O. N. Bossoi and A. Mossa.—p. 91.
*Treatment of Cancer: Inhalations of Vapor of Overheated Ether: Preliminary Note. W. Treuherz.—p. 151.

Treatment of Cancer.—The vapor of overheated ether has been found to have bactericidal effects on tubercle bacilli in cultures (Fornet) and beneficial effects, when inhaled, on cancer and

metastases (Tiegel). This is due to its ability to dissolve cholesterol and lipoids, which are encountered in tubercle bacilli and in tumor tissues. When ether is heated to 60 C. it yields a vapor with 1,722 mm. Hg. of pressure. Before this is administered to the patient it is allowed to expand so that it becomes diluted and cooled to 40 C. The body retains 75% of the inhaled ether, and 25% is eliminated by expiration. The blood serum of patients with cancer absorbs 11 volumes of heated ether vapor while the serum of normal persons absorbs only 1 to 3 volumes. The author administered inhalations of vapor of overheated ether to 43 men and women with very advanced cancer and metastasis. He used Tiegel's technique with his own modifications. Most of the patients were in a desperate condition and had failed to respond to x-rays and radium. The treatment has the following advantages: 1. It is harmless. Neither unpleasant effects nor secondary reactions were observed in more than 500 inhalations administered. 2. In all patients the general condition of health and activity improved; vomiting, anorexia, the subjective symptoms, pain, and hemorrhages disappeared. The patients gained an average of 5.5 kg. in two months. 3. The hemogram improved in some cases. 4. Intestinal tumors became smaller or disappeared. 5. Stenosis of the esophagus disappeared in 20 days in one patient, who had been able to drink only water and who is now able to eat all kinds of food. No changes were noted in the metastases in the bones. The author suggests further work on the effects of vapor of overheated ether and other anesthetics. His article is a preliminary report.

Schweizerische Zeitschrift für Tuberkulose, Basel

8:159-224 (No. 3) 1951. **Partial Index**

Pneumoperitoneum in Treatment of Pulmonary Tuberculosis. S. J. Leitner.—p. 175.

Combination of Intrapleural and Extrapleural Pneumothorax. L. Adelberger and H. Blaha.—p. 193.

*Extrapleural Pneumothorax Combined with Antibiotic Therapy in Pulmonary Tuberculosis with Cavity Formation. E. Herrmann.—p. 205.

Pneumothorax and Antibiotic Therapy.—This paper reports observations on 49 patients with cavernous pulmonary tuberculosis in whom extrapleural pneumothorax was induced in connection with antibiotic therapy. During a preparatory period of at least two months, the patients were treated with paraaminosalicylic acid, and treatment with streptomycin was begun at least four to 10 days before the induction of pneumothorax and was continued during the pneumothorax treatment until the exudate had been absorbed. Comparison of these 49 patients who received combined therapy with 49 who were treated with pneumothorax without the addition of antibiotics during the years between 1939 and 1943 revealed that it was possible to extend the indications for collapse therapy. Other advantages were that the exudate disappeared rapidly, so that the formation of adhesions was prevented and the respiratory function of the noncollapsed portion of the lung was preserved; also, because the pneumothorax does not shrink much, it does not have to be very extensive and thus more of the respiratory surface is preserved. These factors lessen the technical difficulties and reduce the need for secondary plastic operations after the pneumothorax is terminated. The fact that treatment with antibiotics prevents the formation of empyema is highly important, because the empyema not only exerts an unfavorable influence on the immunobiologic condition, but it also makes the pneumothorax rigid and ineffective. The pneumothorax treatment is made simpler and less hazardous by the addition of antibiotics, because limitation of complications reduces the number of refills necessary.

Tubercle, London

32:97-118 (May) 1951

Eosinophilic Lung. L. A. Westwood and S. Levin.—p. 98.

Atelectasis in Pulmonary Tuberculosis. M. Farquharson.—p. 108.

BCG Vaccination in Island of Timor. V. M. Oppers.—p. 111.

Ugeskrift for Laeger, Copenhagen

112:1311-1344 (Sept. 21) 1950. **Partial Index**

*Diverticulitis of Sigmoid Flexure and Perisigmoiditis: Eighteen Cases Treated Operatively. J. J. Jacobsen.—p. 1311.

Operative Treatment of Chronic Hepatitis. J. Ernst.—p. 1317.

*Clinical Observations on Craniotabes: Material from Two Child Welfare Stations in Copenhagen. K. Blom.—p. 1326.

Treatment of Acute Barbiturate Intoxication. J. Røjel.—p. 1335.

Diverticulitis of Sigmoid Flexure and Perisigmoiditis.—Jacobsen discusses 18 cases of complicated diverticulitis and perisigmoiditis treated operatively, in eight men and 10 women, aged 37 to 70. Localized peritonitis was present in one case, vesicocolic fistula in one, peridiverticulitis in two, large extraperitoneal abscesses in two, and stenosing perisigmoiditis in seven. Of the eight postoperative deaths four were due to diffuse peritonitis and four to intoxication and poor general condition. In addition to the danger of local complications in these cases the presence of an infectious focus in the organism involves the risk of septic complications. The first step in the treatment of perisigmoiditis should usually be the formation of an artificial anus; further treatment depends on the complications. In most cases there were multiple symptoms. In perisigmoiditis differentiation from cancer of the colon is difficult. While roentgen examination affords valuable information, it rarely gives certain diagnosis. Diverticulosis is not believed to predispose to cancer of the colon, but because of the frequency of the two affections they will occasionally occur together.

Craniotabes.—Blom reports that of 662 children examined at two children's welfare stations 83 (12.6%) had craniotabes. The results support the assumption that craniotabes is not of rachitic but is of physiological nature. Prophylactic administration of cod liver oil to mothers and children did not prevent craniotabes but prevented rickets. Craniotabes is thought to be an osteoporosis due to high growth intensity. The parietal bones are most commonly affected, perhaps as the place of least resistance, since they are exposed for the longest time to the greatest intrauterine and postnatal pressure.

Wiener medizinische Wochenschrift, Vienna

101:299-322 (April 28) 1951. **Partial Index**

*Clinical Results, Technique and Pathological Anatomy of Procaine Hydrochloride Infiltration of Frontal Cerebral Lobe in Cancer Patients with Intractable Pain. F. Mandl, F. Paul, W. Gyri and R. Jelinek.—p. 304.

Atrophy of Neck of Femur. A. Saxl.—p. 308.

Procaine Infiltration of Frontal Lobe for Relief of Intractable Pain.—Fourteen patients with carcinoma of the uterus, larynx, and rectum, and bronchial carcinoma submitted to procaine hydrochloride infiltration of the frontal cerebral lobe. An injection of up to 15 cc. of a 1% solution of procaine hydrochloride was made through a trephine opening in the sagittal plane from a point 3 cm. in front of the coronal suture and 3 cm. laterally from the midline toward the upper orbital vault. In most of the patients intervention was performed on the ipsilateral side to the focus of pain. Results were excellent or satisfactory in seven patients, encouraging in three, doubtful in one, and poor in three. The complications sometimes following lobotomy did not occur in any of the patients. Three patients who obtained only temporary relief from pain (partial results) required repeated infiltration, which was performed transcutaneously through the old trephine opening except for one patient in whom ossification of the old opening had occurred within five weeks. Experiments on cadavers with a solution of methylene blue for infiltration of the frontal lobe showed that there was no discoloration of the adjacent portions of the brain. The stain spread only over the convexity and over the base of the brain. Additional experiments on cadavers demonstrated that infiltration with the described technique is not dangerous and that the injection needle is never in contact with the anterior horn of the lateral ventricle. Necropsies performed on four patients demonstrated that the pressure of the injected solution produces a mechanically conditioned, hemorrhagic softening of the brain substance, the extent of which apparently varies with the amount of pressure applied. It is suggested that the analgesic effect of the infiltration may be due to this destruction of the pathways in the frontal lobe and probably does not depend on the type of the anesthetic used.

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QUERIES AND MINOR NOTES

ADIE'S SYNDROME

TO THE EDITOR:—*A woman, 43, an immigrant from Germany, was first seen Sept. 2, 1950, complaining of increasing night blindness for two months, without other ocular or systemic symptoms. Past history revealed hypertension to 170 systolic, treated with pills in Germany, a tonsillectomy performed one year ago for recurrent "sore throat," and one full term normal pregnancy. The patient's weight is 143 lb. (64.9 kg.) and her blood pressure is 150/90, left arm, sitting. The pupils are equal and react normally to light and accommodation. The visual fields are normal by confrontation; the visual acuity is 20/20 bilaterally. The fundi are normal. Neurological examination is normal, except that knee and ankle jerks are absent. The hemoglobin is 13 gm. The blood smear is normal. On Oct. 21 the patient stated that friends had noted unequal pupils and that night blindness was unchanged. The left pupil was found to be larger than the right, and the left pupil had no direct or consensual reaction to light, or to accommodation. Results of a Kline blood test had been reported negative. On Feb. 17, 1951, a spinal puncture was done, revealing clear fluid, with one lymphocyte. The fluid was Nonne negative, the total protein 32 mg. per 100 cc., and the Wassermann and colloidal reactions negative. Routine skull x-rays, taken the same day, were normal. This was considered to be a case of Adie's syndrome.*

John T. Harbaugh, M.D., St. Paul.

ANSWER.—The diagnosis of Adie's syndrome in this case is certainly correct. The majority of affected persons are females who are apparently healthy otherwise. The onset is usually sudden, and the condition is permanent. The size of the tonic pupil, however, varies from time to time and may even become smaller than its mate. The tonic pupil is unilateral in 80% of cases and most often left-sided, as in this patient. Unlike the true Argyll Robertson pupil, the tonic pupil dilates normally with mydriatics (atropine, homatropine, cocaine). In 1940 Scheie introduced a specific test, the reliability of which has since been firmly established. The instillation of 2.5% methacholine produces a contraction of the tonic pupil, whereas the normal pupil is not affected by this concentration. The hypersensitivity of the tonic pupil to cholinergic drugs apparently indicates that the lesion is in the ciliary ganglion or is peripheral thereto.

Adie thought the affection was due to a disease of the vegetative nervous system. Lowenstein and Friedman consider the malady a heredodegenerative disturbance affecting the vegetative centers of the diencephalon and their connections with the mesencephalon. James ascribed the condition to general nervous asthenia. Jeliffe observed a tonic pupil and areflexia (loss of knee and ankle jerks) in a woman with hypothyroidism, which responded to the administration of thyroid. Kennedy showed that the syndrome may be associated with anxiety neurosis and that freedom from nervous tension in such instances resulted in improvement.

In the case cited the therapeutic test indicated that the night blindness was not due to avitaminosis. Night blindness due to vitamin A deficiency is usually observed in persons less than 20 years old and is extremely rare in this country. Night vision is normally best if the refractive status is that of mild hyperopia. The tonic pupil may be associated with tonic accommodation and consequent adventitious myopia. Night blindness is frequent in all neurotic cases, especially anxiety neuroses, in which a reversion to the childhood fear of darkness evidently occurs. In the recent war night blindness of this type assumed almost epidemic proportions in the combatant armies.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any official bodies unless specifically stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

PUPILLARY INEQUALITY

TO THE EDITOR:—*A 7 year old girl, under treatment for migraine which centered around the right eye, was referred to me because of a dilated right pupil which reacts minimally to light and has apparently normal accommodation. Vision is 20/20 with or without a minimal hyperopic astigmatic correction. There was no apparent change in the right pupil before or after cycloplegic examination. The Wassermann reaction, sedimentation rate, results of neurologic examination, and routine skull x-rays were normal. There is no history of trauma. The child is apparently normal except for this dilated right pupil. Does Adie's syndrome occur in children? Would a vascular entity cause more symptoms?*

M.D., Minnesota.

ANSWER.—Adie's syndrome has been observed in a child 5 years of age, in whom pupillary inequality was observed at 6 months. The syndrome is characterized by unilateral enlargement of the pupil with the direct and indirect light reflex almost completely abolished. The pupil further dilates in the dark and slowly contracts in a brightly illuminated room. During accommodation-convergence after a delay which may be as long as five minutes, the abnormal pupil slowly contracts until it may be smaller than the fellow pupil. There may be an associated loss of tendon reflexes. The tonic pupil contracts with 2.5% methacholine, which does not affect the normal pupil in this concentration.

Analysis of the cause of the pupillary dilation in this patient requires the following additional information: (1) length of time condition has been present; (2) nature of the migraine; (3) range of accommodation in each eye; (4) direct and indirect light reflex of both eyes; (5) fields of vision, and (6) pharmacologic response of the pupils. The following conditions are suggested: (1) Adie's syndrome, (2) ophthalmoplegia interna, (3) paralytic mydriasis, (4) congenital mydriasis, and (5) adrenergic nerve irritation.

An excellent review of the pupillary reflexes and their abnormalities is contained in the work by Walsh (Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947).

IMPAIRED HEARING

TO THE EDITOR:—*One of my ears has incurable nerve deafness. Every winter my other ear becomes affected with eustachian closure, with resulting partial deafness. This clears up within a month or so, and hearing improves. I have had four treatments with radon applicators over the fossae of Rosenmueller (three years ago) with great relief. The attacks now last longer and are not so amenable to treatment. I have desensitized myself with graduated histamine injections and recently seemed to be helped with 100 mg. of cortisone in tablet form for two days. What is the present accepted treatment in this disturbing condition? What is the prognosis? What climate is most favorable in prevention of the annual recurrence of this apparently seasonal (damp weather) condition?*

M.D., New York.

ANSWER.—Impaired hearing due to eustachian tube closure may be caused by hypertrophied adenoidal tissue around the tubal orifice; by an allergy, particularly to house dust; by neoplasm in the nasopharynx (usually carcinoma), and by temporomandibular joint malocclusion as a result of replacement of the molar teeth with dentures that do not give the proper support to the bite.

The treatment of eustachian tube occlusion is removal of the causative factor, if possible, and inflation of the eustachian tubes. If there is an accumulation of serum in the middle ear, paracentesis followed by inflation may be indicated. In this case, an allergy to house dust would seem possible, in which case desensitization with minute dosage therapy, as described by Hansel,

would be worth trying. In cases of allergy to house dust, the best climate is one with warm, clean air, best found in southern Florida or the Caribbean Islands rather than in New Mexico or Arizona, where there is much dust.

The prognosis is generally good, although rare cases may be very resistant to treatment. As a rule, the hearing can be restored to normal by establishment of normal ventilation of the eustachian tube. Rarely, in long-standing cases, permanent adhesive changes in the middle ear develop, with a permanent hearing impairment.

TESTS FOR CORONARY INSUFFICIENCY

To the Editor:—*I would greatly appreciate it if you would have several competent authorities discuss the relative merits of the Levy test and the Master test, which are used in the detection of coronary insufficiency in patients whose histories are not definite enough to make such a diagnosis from their symptoms. I would appreciate a discussion of the use of these tests in the detection of "latent" coronary insufficiency in patients who give no history suggesting coronary insufficiency but in whom it is desired to ascertain an accurate picture of their coronary function prior to their undergoing strenuous physical effort.* *M.D., Washington.*

Answer.—The anoxemia (Levy) and exercise tolerance (Master) tests are used to induce a relative lack of oxygen supply to the myocardium. The former does so by producing hypoxemia secondary to inhalation of a low oxygen-gas mixture; the latter increases the work of the heart and thus, in conditions where coronary blood flow cannot be increased sufficiently, leads to relative coronary insufficiency and hence a decreased oxygen supply to the heart. Since both tests utimately evaluate the same functional deficiency and vary only in the manner of its production, many of their indications, merits, and demerits are the same. Both tests should be conducted only by well qualified physicians, because of the inherent danger of producing arrhythmias and even myocardial infarction. The anoxemia test requires special, although relatively simple equipment, while the two-step exercise tolerance test requires only a wooden step. The anoxemia test has the advantage of immediately providing 100% oxygen inhalation, if necessary, while the exercise, once performed, may continue to increase the work of the heart even when the exercise is stopped. On the other hand, the exercise tolerance test simulates the type of strain on the heart that so often produces the symptoms in the patient. From wide experience in the past, the exercise tolerance test is well standardized in terms of the number of steps to be taken and of electrocardiograms that are considered "positive." It is the opinion of many physicians who have used both that the anoxemia test is more dangerous and also less comfortable for the patient.

Even without previous symptoms, these tests may show abnormal results in a given patient. Such results should certainly be taken as a warning against strenuous physical effort. However, the normal response to either of these tests should not per se exclude the possibility of coronary insufficiency, and the patient's condition as a whole must be considered. "False negatives" certainly occur, even in patients with proved coronary disease. "False positive" tests, such as are reported in anxiety states, are rare.

ACID SALTS AND EDEMA

To the Editor:—*A hypertensive patient has had a coronary and recurrent decompensation. It has been necessary to give mersalyl (salyrgan®) intravenously almost daily to keep ahead of his edema. In desperation the family tried a home remedy of boric acid crystals and cream of tarter mixed with water and taken by mouth. Surprisingly, this concoction has kept the patient free from edema for two weeks. I am curious to know whether there is any scientific background for such therapy.* *Archie S. Narotzky, M.D., Ishpeming, Mich.*

Answer.—Acid salts have been used for years in the treatment of nephrotic edema. It may well be that boric acid crystals and potassium acid tartrate have a diuretic effect, due not only to their acid properties but also to the potassium. Ever since Bunge's original work in the last part of the 19th century, which showed the antagonism between the retention of sodium and potassium, potassium has been used in the therapy of patients with edema. Without the dosage of either the boric acid or cream of tartar being specified, comment on the advisability of the therapy used is difficult. Serious poisoning can result from the ingestion of 5 gm. of boric acid. The toxic effects include nausea, vomiting, abdominal pain, diarrhea, visual disturbances, renal injury, collapse, and, occasionally, death. Its use in a chronic condition would appear to involve considerable risk. Tartrates are poorly absorbed from the gastrointestinal tract and are therefore sometimes employed as cathartic. If tartrates are absorbed into the circulation, they may produce renal damage. Cream of tartar, therefore, in the treatment of a chronic renal condition, would also appear to involve considerable risk. It seems pertinent to remark that injury to the kidneys of an edematous nephrotic patient may result in a diuresis, with the impression of improvement in the renal disease though the apparent beneficial effect is the result of accentuation of renal disability.

DAMAGE CAUSED BY BORON COMPOUNDS

To the Editor:—*Can either allergic rhinitis or dermatitis of the face be produced in industry where both boric acid and borax particles fill the air?* *M. H. Brodkey, M.D., Omaha.*

Answer.—Repeatedly since 1881, boron compounds have been reported as causative of both surface and systemic damage. Injury has followed ingestion, hypodermic injection, enemas, pleural lavage, ointment application, and industrial exposure. Hypersusceptibility is the rule, but susceptibility did not enter as a factor in a series of fatal cases in which boric acid solution accidentally was substituted for water in nipple bottles for infants. Exposure may be acute or chronic, and the consequences likewise may be acute or chronic. Currently the commonest lesion is that of eczematous dermatitis, with the chief location about the face. Present day concepts of sensitization imply that almost any agent capable of producing a surface lesion may, through tissue damage, create a specific allergy. On this basis a boron-induced allergy becomes tenable, but this is not the usual form of damage.

TINNITUS

To the Editor:—*In 1949, while flying with a mild head cold, I contracted aero-otitis; ever since I have had a soft humming sound in both my ears and at times a feeling of fulness. Six months later, I had some x-ray treatment to both ears involving 40 r on three or four occasions, in an attempt to shrink the lymph nodes in the posterior pharynx. This did not help. I then had a complete physical examination, with no pathological findings; my hearing was perfect. I have noticed that my ear condition definitely depends on humidity changes; during dry days I am about free of humming sounds and fulness. I shall appreciate greatly information on treatment. I am 40 years of age.*

M.D., Indiana.

Answer.—Tinnitus is a symptom of various types of middle and inner ear pathology. When there is a reversible condition, such as aero-otitis, suppurative otitis media, or perforated tympanic membrane, the tinnitus is frequently relieved by relieving the underlying condition. More often there is no reversible pathology in the inner or middle ear, and in these cases there is no effective treatment for tinnitus. Since, in your case, the aero-otitis has long since cleared up, the tinnitus would fall into the latter classification.

THIAMINE INJECTIONS FOR FIVE YEARS

To the Editor:—*For five years a bank executive has had three or four hypodermic injections weekly of thiamine hydrochloride in 100 mg. doses without any apparent detrimental reactions. He claims it energizes him. Is there any danger in the continuous use of this vitamin?* *M.D., New York.*

Answer.—Thiamine hydrochloride is believed to have no toxic effects. The requirement for the average person is small, perhaps less than 2 mg. daily. When needed, however, this vitamin is given in much larger amounts, often 100 mg. or more

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daily. As much as 25,000 times the actual requirement has been given without harmful effect. The amount taken by this patient, 100 mg. four times weekly could apparently have no harmful effect. However, one wonders about the continuance of this procedure for five years. There is a psychological element here that cannot be ignored. Why not advise him to get his vitamins from food?

NICOTINAMIDE

To the Editor:—*Why does nicotinamide relieve certain cases of vertigo? Has nicotinamide ever been reported to produce undesirable symptoms in heavy doses? Would 200 mg. four times daily be considered an overdose? Could 400 mg. daily by mouth for three weeks produce precordial pain and constriction referred to the left side of the back?*

M.D., New Jersey.

Answer.—Vertigo may be one of the symptoms of pellagra, and in such cases the administration of nicotinamide would be of help. "Undesirable symptoms" have not been reported as resulting from reasonably heavy doses of this substance. A dose of 500 mg. each 24 hours is regarded as a good average amount, but 1 gm. daily has been given over a period of several weeks without injurious effects. The substance is usually well borne. There appear to be no reports of intolerance to its continued administration which would produce "precordial pain and constriction referred to the left side of the back."

PSORIASIS IN A VIOLINIST

To the Editor:—*A male violinist, 25, wishes to study the instrument in order to play it professionally. He has a patch of psoriasis on an elbow, two on the occiput, and has slight psoriatic involvement of three nails of each hand. His mother has psoriasis, but there is no family history of rheumatoid or psoriatic arthritis. He states that if arthritis is likely to develop in the ratio of 1 to 5 he will discontinue his study now rather than gamble on being disabled later, after years of working toward eminence. What is the incidence of psoriatic arthritis in the finger joints of persons who have psoriasis of the nails?*

M.D., California.

Answer.—Both psoriasis and arthritis are common diseases. For one to determine the relative incidence of psoriatic arthritis as compared to other types of arthritis, a long-term study of innumerable patients with both diseases would be required. Then, too, the clinical course of psoriasis is unpredictable. Fortunately, in most cases, the psoriasis constitutes little more than a cosmetic problem. There seems to be no reason to suspect arthritis of the finger joints to develop oftener in persons with psoriasis of the nails. If this young man has unusual talent and a great desire to become an eminent violinist, he should be encouraged to continue his studies.

NEPHROTIC SYNDROME

To the Editor:—*A 44 year old white woman has acute glomerular nephritis of two months' duration, which has now entered a nephrotic stage with reversal of the albumin-globulin ratio, constant albuminuria (4 plus) and moderate edema which cleared with bed rest and salt-free diet. Is the use of pituitary adrenocorticotropic hormone (ACTH) or cortisone indicated?*

John M. Butcher, M.D., Sarasota, Fla.

Answer.—The place that cortisone and pituitary adrenocorticotropic hormone will finally occupy in the treatment of acute glomerulonephritis or the nephrotic syndrome has not yet been established. Some investigators report good results, whereas in other hands these hormones have resulted in definite metabolic changes without apparently influencing the course of the disease. Patients with the nephrotic syndrome who have apparently had good results have, in certain instances, subsequently had a recurrence of edema. If edema can be controlled by dietary and other established measures, then this would be preferable, as there is no evidence that these hormones remove the renal lesion.

BYSSINOSIS

To the Editor:—*I have an industrial case with a question of death being secondary to byssinosis. Can you give me any information regarding this?*

M.D., Michigan.

Answer.—Byssinosis, commonly called "mill fever," is a pulmonary infection of low severity arising among cotton mill workers, chiefly in Europe. This disease has been variously associated, as to cause, with bacterial and fungal infection, allergy, and the toxin of Aerobacter cloacae (Prausnitz, C.: Medical Research Council; Special Report Series, No. 212, His Majesty's Stationery Office, 1936; Bolen, H. L.: *J. Indust. Hyg. & Toxicol.* **25**:215 [June] 1943).

PSORIASIS

To the Editor:—*A young woman began taking capsules of undecylenic acid for psoriasis, and after two days, complained of a rash of fine small punctate erythematous macules and papules on the face, neck and forearms. The patient being of a nervous disposition, I advised discontinuance of the undecylenic acid, pending inquiry, and substituting tripelennamine hydrochloride locally and internally. 1. Can one expect that such rash would disappear along with the old psoriasis lesions if one disregards these new papules and continues the undecylenic acid treatment for psoriasis? 2. Does undecylenic acid aggravate or precipitate new lesions? These are too immature to identify as psoriasis. 3. Is ACTH or cortisone to be regarded as the best available treatment of psoriasis? 4. Has aureomycin caused an allergic rash?*

W. J. Wakefield, M.D., Vienna, Ill.

Answer.—Experience in a large series of patients shows that undecylenic acid has no value whatsoever in the treatment of psoriasis. In some patients the psoriasis apparently has been aggravated by the use of undecylenic acid. Pituitary adrenocorticotropic hormone (ACTH) or cortisone relieves the patient of the psoriasis temporarily; however, when the drug is discontinued the psoriasis recurs, sometimes more extensively than before treatment was started. Aureomycin has produced few cutaneous reactions.

CHLOROPHYLL

To the Editor:—*What is the scientific explanation for the use of chlorophyll as a deodorant when taken internally and when used in the form of an airwick for odors in a room?*

G. Horace Coshow, M.D., Carpinteria, Calif.

To the Editor:—*Is there any known harmful effect if chlorophyll is taken internally for purposes of deodorizing secretions or breath? Is there a maximum daily dosage? If there are any known harmful effects, what organs may be affected?*

W. F. Holmes, M.D., Walla Walla, Wash.

Answer.—Chlorophyll as it occurs in plants is unstable, and the commercial preparations used as deodorants are modified derivatives of the green coloring matter of plants. Studies by Moss, Morrow, Long and Ravdin (*J. A. M. A.* **140**:1336 [Aug. 27] 1949) have shown that a chlorophyll derivative will deodorize foul-smelling wounds. This action did not appear to be due to destruction of bacteria, since this chlorophyll preparation was not an efficient antiseptic. The apparent mechanism of action is probably one of adsorption or possibly oxidation or reduction of the odorous substances.

No satisfactory explanation has been offered for the deodorant effect of orally administered chlorophyll derivatives reported by Westcott (*New York State J. Med.* March 15, 1950). Kohler, Elvjehem and Hart (*J. Biol. Chem.* **128**:501 [May] 1939) reported that chlorophyll was not absorbed from the gastrointestinal tract, and there is no evidence available as yet that identifiable derivatives of chlorophyll are present in body fluids or in the urine after ingestion of chlorophyll.

It is generally believed that most body odor is due to bacterial decomposition of sebaceous secretions on the skin. There is no evidence that chlorophyll decreases this secretion or alters the bacterial flora of the skin. Furthermore, satisfac-

tory control tests have not been made with chlorophyll taken internally as a deodorant; thus, not only is the mechanism of action unexplained, but it is not at all certain that the action exists except in the mind of the observer.

There is no evidence that chlorophyll or the available derivatives have any harmful action. Furthermore, it should be remembered that chlorophyll is a fairly constant constituent of a well balanced diet which includes green vegetables. Finally, one should consider the fact that many herbivorous animals, including the goat, consume large quantities of chlorophyll, and some of these are noted for their pungent aroma.

ALOPECIA UNIVERSALIS

To the Editor:—*What treatment, if any, is available for alopecia universalis? I have in mind a woman, 50, who suddenly lost all the hair on her body, probably from a severe mental shock.* *Edward B. Tyson, M.D., Ocean City, N. J.*

Answer.—The treatment of alopecia universalis is altogether unsatisfactory. One occasionally observes some spontaneous regrowth of hairs, and at times one hears of an encouraging result from the use of hormone therapy. In general, however, the cause is obscure and treatment meets with failure.

PREGNANCY FOLLOWING ILEOSTOMY

To the Editor:—*A woman, 27, has one living child, 5 years. Since the birth of this child, the patient has had a permanent ileostomy, because of colitis, with a complete colectomy. She is desirous of becoming pregnant again. Would there be any danger in any way if she becomes pregnant?*

Nerio W. Pioppi, M.D., Southbridge, Mass.

Answer.—This patient may safely become pregnant and be permitted to have a vaginal delivery. A case report entitled "Successful Pregnancy Following Ileostomy with Partial Colectomy for Ulcerative Colitis" was published by Kenneth W. Warren in the *Lahey Clinic Bulletin* (**5**:202 [Jan.] 1948).

THE OSCILLOMETER AND SKIN TEMPERATURE MEASUREMENTS

To the Editor:—*What errors are associated with the use of an oscillometer, and how accurate is this machine in detecting suspected peripheral arterial disease? Are fewer errors apt to be associated with skin temperature measurements?*

Paul Russell, M.D., Inglewood, Calif.

Answer.—Assuming that the oscillometer is mechanically correct, it registers occlusion or loss of elasticity in the pulsatile part of the peripheral arterial tree; the height and the shape of the oscillometric curve, together with the visible thrust or worm-like movement of the needle, permit a great many conclusions by an experienced observer, especially if differences are detected at symmetrical levels of the two extremities. The instrument does not detect any changes in digital circulation or disturbances in arteriolar flow. Skin temperature measurements, in the absence of a room with controlled temperature and humidity, can have only comparative value when one symmetrical area is tested against the other or when the effects of release of vasomotor tone is studied.

DWARFISM

To the Editor:—*The answer to a query in the June 16, 1951, issue of* The Journal *did not fully explore the diagnostic possibilities in the case of an underdeveloped child with glycosuria, despite a normal blood sugar content, and albuminuria in the presence of an otherwise normal urine. In the answer, it was presumed that renal dwarfism existed. However, a rare hereditary defect of the proximal tubules of the kidney has been described by Fanconi which could explain the findings noted in the above case. In the Fanconi syndrome there is a defect in the phosphorylating mechanism with resultant inability to reabsorb glucose, amino acids, and phosphate from the glomerular filtrate. This leads to a loss of these substances in the urine and a negative nitrogen and phosphorus balance with consequent impaired growth, underdeveloped musculature, and osteoporosis. Fractures can occur from minor trauma, and prolonged fasting can produce hypoglycemic symptoms. McCune and co-workers reviewed the literature of this disorder (Am. J. Dis. Child.* **65**:*81, 1943).*

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PERSISTENT SALTY TASTE

To the Editor:—*In* The Journal, *June 16, 1951 (page 689), Dr. Robert A. Marks asks for the cause of a persistent salty taste in the mouth of a 57 year old white man. He stated that the symptoms started after teeth had been removed for "pyorrhea," and persisted after he was fitted with a full upper and lower denture. The most likely cause was omitted in the answer. A persistent salty taste in the mouth is caused by an antral-oral fistula until proved otherwise. Such fistulas may be difficult to locate, as they are often in a tissue fold under the denture. The salty taste is caused by the secretions of the maxillary sinus entering the oral cavity. Before this man is sent to a neuropsychiatrist, as is suggested in the answer, he should be sent to a competent oral surgeon who could determine whether such an antral-oral fistula is present. This is especially likely in this case because it occurred after the removal of teeth for "pyorrhea" (a better term is periodontoclasia). It is also stated in the answer that there may be a "lowered sensitivity to taste—especially if the palate is covered by a plate." There are no taste buds in the hard palate which is covered by a denture. The answer to a query in* The Journal *of Sept. 17, 1949 (page 237), regarding a salty, bitter taste also omitted the statement that salty taste is almost pathognomonic of an antral-oral fistula.*

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IMMUNITY AGAINST DIPHTHERIA

To the Editor:—*I am taking the liberty of writing an addendum to the reply to a query in* The Journal *on immunity against diphtheria (April 8, 1950, page 1115). While there is no doubt that toxoid is effective in stimulating the appearance of antitoxin in the blood, there is considerable evidence that this does not necessarily confer immunity. There is far too much tendency to confuse "antitoxin in the blood stream" with immunity and to use the two terms interchangeably. That antitoxin in the blood does not necessarily confer immunity is shown by the development of diphtheria in persons receiving antitoxin a short time before onset. There are also several reports of diphtheria in many persons supposedly adequately "immunized" (Schick negative) with toxoid (Merkel, A. E.: An Outbreak of Diphtheria in Medford, Oregon, 1949, Am. J. Pub. Health* **41**:*522, 1951). On the other hand, many normal adults (around 30%) give a positive reaction to the Schick test; yet diphtheria is uncommon in adults even when they have been exposed to the disease (although there is some indication that the age distribution of the disease may be higher than formerly). Of much greater significance in immunity to diphtheria is "tissue resistance," an allergy-like, binding reactivity of tissues toward the diphtheria bacilli themselves. This is very potent and is wholly independent of antitoxin. (Frobisher, M., Jr., and Parsons, E. I.: Studies on Type-Specific Immunization with Somatic Antigens of Corynebacterium Diphtheriae, Am. J. Hyg.* **52**: *239, 1950).*

With respect to the query referred to above, I believe that the immunity to diphtheria that follows the natural disease is far more effective than that which follows injections of bacillus-free toxoid because the patient develops "tissue resistance" as a result of contact with the bacilli, as well as antitoxin resulting from contact with toxin. This is the reason that, as pointed out in the previous reply to the query, "Authentic second attacks of diphtheria are rare."

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